POSITRON EMISSION TOMOGRAPHY IN QUÉBEC

Prepared by:

François-Pierre Dussault
Van H. Nguyen
Fatiha Rachet

(AÉTMIS 01-3 RE)

Report submitted to the

Québec Minister of Research, Science and Technology

This assessment is an official report produced and published by the *Agence d'évaluation des technologies et des modes d'intervention en santé* (*AÉTMIS*). It is also available in PDF format on the Agency's Web site.

Information concerning this report or any other report produced by *AÉTMIS* may be obtained by contacting it at:

Agence d'évaluation des technologies et
des modes d'intervention en santé (*AÉTMIS*)
2021, avenue Union, bureau 1040
Montréal (Québec) H3A 2S9

Telephone: (514) 873-2563
Fax: (514) 873-1369
E-mail: aetmis@aetmis.gouv.qc.ca
Web address: http://www.aetmis.gouv.qc.ca

How to cite this report:

Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS). Positron emission tomography in Québec. Report prepared by François-Pierre Dussault, Van H. Nguyen and Fatiha Rachet. (AÉTMIS 01-3 RE). Montréal: AÉTMIS , 2001, xviii-270 p.

Legal deposit
Bibliothèque nationale du Québec, 2001
National Library of Canada, 2001
ISBN 2-550-37972-1

© Gouvernement du Québec, 2001

This report may be reproduced in whole or in part, provided the source is cited.

Québec

Agence d'évaluation
des technologies
et des modes
d'intervention en santé

MISSION

To assist the Minister of Research, Science and Technology and the policymakers in Québec's health-care system, including the Ministère de la Santé et des Services sociaux, by means of health technology and health intervention modality assessments, specifically, by assessing their efficacy, safety, costs and cost-effectiveness, and their ethical, social and economic implications.

To assist the Minister of Research, Science and Technology in developing and implementing scientific policy.

THE AGENCY'S MEMBERS

Renaldo N. Battista, M.D.
President and Chief Executive Officer

Jeffrey Barkun
Physician (surgery)

Marie-Dominique Beaulieu
Physician (family medicine)

Suzanne Claveau
Physician (microbiology/infectious diseases)

Roger Jacob
Biomedical engineer

Denise Leclerc
Pharmacist

Louise Montreuil
Administrator

Jean-Marie Moutquin
Physician (obstetrics and gynecology)

Réginald Nadeau
Physician (cardiology)

Guy Rocher
Sociologist

Lee Söderstrom
Economist

SCIENTIFIC DIRECTOR

Jean-Marie R. Lance

POSITRON EMISSION TOMOGRAPHY IN QUÉBEC

Positron emission tomography (PET) is a noninvasive medical imaging technique. It provides information on the location and metabolic activity of tissues and lesions, which distinguishes it from most other medical imaging techniques, which provide mainly anatomical information.

Originally a research tool, PET is being used more and more in clinical settings, with the issue of coverage now facing most public and private health insurance plans.

With this backdrop, the Fédération des médecins spécialistes du Québec and the Conseil québécois de lutte contre le cancer asked the *Agence d'évaluation des technologies et des modes d'intervention en santé* (*AÉTMIS*) to examine the appropriateness of deploying PET for clinical purposes in Québec, where there are already two mainly research-oriented centres equipped with this technology.

AÉTMIS observed that, while the list of clinical uses is growing, the formal assessment reports on the efficacy and cost-effectiveness of PET are cautious about the strength of the hard data. Nonetheless, a good number of clinical uses of PET are recognized in oncology, neurology and cardiology. There are several other, potential or nonrecognized uses in these fields (data incomplete or nonexistent).

The hard data nonetheless seem sufficient for recommending the deployment of PET in Québec for certain clinical uses. A ministerial master plan should govern this deployment, taking into account the population's clinical needs and the specialized human and physical resources that this technology requires. Furthermore, this deployment should be accompanied by research, training and validation and take place in close collaboration with university hospital centres and university institutes.

In disseminating this report, *AÉTMIS* wishes to provide the best possible information to the policymakers concerned by this topic at different levels in Québec's health and social services system.

Renaldo N. Battista
Chief Executive Officer

SUMMARY

CONTEXT AND OBJECTIVES OF THIS REPORT

This assessment report was undertaken following a joint request from the Fédération des médecins spécialistes du Québec (FMSQ) and the Conseil québécois de lutte contre le cancer (CQLC) concerning the clinical efficacy of a recent medical imaging technology, positron emission tomography (PET). Over the past decade, the use of PET for diagnostic and therapeutic guidance and monitoring purposes has increased considerably. The *Agence d'évaluation des technologies et des modes d'intervention en santé* (*AÉTMIS*) undertook to: a) gather hard data on the clinical use of PET in different fields, in particular, oncology, neurology and cardiology; and b) to make recommendations concerning the possible deployment of PET in Québec. While carrying out this project, *AÉTMIS* relied on the collaboration of an advisory committee consisting of representatives from the FMSQ, the CQLC and the Ministère de la Santé et des Services sociaux (MSSS) and other health technology assessment specialists. It should be noted that this report examines only the clinical uses of PET, to the exclusion of its research applications.

POSITRON EMISSION TOMOGRAPHY

Introduced as a research tool in the mid-70s, PET differs from other medical imaging technologies in that it enables one to study the metabolic activity and blood flow in tissues. PET requires the administration of radiopharmaceuticals labelled with positron-emitting isotopes. For example, FDG (fluorodeoxyglucose), the substance currently used most often in PET scans, incorporates a radioactive isotope, fluorine-18. These isotopes are produced by cyclotrons. Three-dimensional images are obtained by detecting photons created during positron emission and by interpreting them using a complex imaging system.

Most of the isotopes used in positron emission tomography have a very short half-life (e.g., 2 minutes for oxygen-15 to 110 minutes for fluorine-18). Facilities that offer PET services must therefore have a cyclotron or be close enough to one to be able to transport isotopes within a reasonable amount of time.

In Québec, there are already two mainly research-oriented PET facilities with a cyclotron, one at the Montreal Neurological Institute (MNI), the other at the Centre hospitalier universitaire de Sherbrooke (CHUS). Québec currently ranks average among the industrialized countries in terms of the number of PET facilities per capita. Ontario, British Columbia and, as of 2001, Alberta have PET facilities as well.

STUDY METHODOLOGY

As part of this study, *AÉTMIS* did a review and synthesis of the hard data on the clinical efficacy of PET. The assessment was based on data from reports published by assessment agencies and reports from organizations containing recommendations concerning PET scan coverage and on publications postdating those reports. The publications were chosen on the basis of criteria adapted from reliable protocols.

As was the case for several other medical imaging technologies, the clinical use of PET developed before its efficacy and efficiency were demonstrated. The fields of application of PET continue to evolve, thanks to the contribution of research. Furthermore, the rapid pace of technological improvements to PET are an obstacle to acquiring hard data to be used for assessment purposes. In fact, the list of uses whose clinical efficacy is recognized is growing by the day. Lastly, the use of PET is developing in a complementary fashion with a panoply of medical imaging technologies, which are evolving rapidly as well. This assessment was not aimed at documenting the evolution of the related technologies.

CLINICAL UTILITY OF PET

AÉTMIS's study confirms the clinical utility of PET in many oncological, neurological and cardiological applications. For example, in oncology, the PET's utility is recognized in certain specific applications in lung cancer, colorectal cancer, melanoma, head and neck cancer, and lymphomas. Depending on the type of cancer, PET is used for diagnostic purposes, for detecting metastases and for monitoring response to therapy. In neurology, PET is recognized to be effective in certain uses in epilepsy and brain tumors. In cardiology, its utility is recognized in certain applications, such as myocardial viability and myocardial perfusion studies. Lastly, PET has promising potential for other uses in these areas of practice.

There are few data on the efficiency of PET, except for some partial data for non-small-cell lung cancer, to cite one example. This is why models have been constructed exclusively for the applications in this type of cancer and those for evaluating myocardial viability. These models suggest that PET is cost-effective in these cases.

SUGGESTIONS FOR DEPLOYING PET IN QUÉBEC

Since the list of recognized or potential uses of PET is constantly growing, it is difficult to accurately determine the number of patients who could benefit from this technology in Québec. However, based on opinions expressed within the advisory committee, the number of scans required could tentatively be estimated at 15,000 or more a year. Based on this estimate, the clinical needs seem sufficient for justifying the timely deployment of PET for certain uses in oncology, cardiology and neurology.

These estimated needs can only be met gradually. In ordinary operating conditions, the deployment of PET would require about 10 to 15 scanners supplied by 3 or 4 cyclotrons (including those already in operation). Based on the implementation scenarios chosen, the overall cost of deploying additional PET resources would be between several tens of millions of dollars and more than about hundred million dollars.

Gradual deployment is all the more necessary because operating a PET centre requires specialized physical and human resources. Presently, there are not enough human resources specifically trained in PET in Québec to sustain the proposed deployment. Training such resources should therefore be a priority.

A ministerial master plan should govern the deployment of PET, taking into account the clinical needs and specialized physical and human resources (existing or to be developed) that this technology requires.

RECOMMENDATIONS

Deployment

- Since the clinical efficacy of PET is recognized in many oncological, cardiological and neurological applications, it would be advisable to promote and sustain the deployment of PET for clinical purposes in Québec's public health-care system.
- PET scans should be available on a priority basis for the clinical applications with recognized clinical efficacy. These applications should be reviewed periodically as new hard data reflecting the rapid devel-

opment of relevant information become available.

Deployment Specifics

- A master PET deployment plan should be prepared by the Ministère de la Santé et des Services sociaux.

- The plan should involve quantifying the population's PET scan needs both with regard to optimizing the other existing technologies and to PET requirements for which human and physical resources could sometimes prove to be a limiting factor. The plan should therefore be prepared both in collaboration with the existing PET centres, whose expertise could be put to good use, and in consultation with the different players in tertiary intervention settings.

- The plan should take into account the fact that PET cannot be deployed for clinical purposes without conducting research into the promising applications that are presently recognized as having potential but whose efficacy and cost-effectiveness have not yet been demonstrated.

- Since the plan should involve assessing the efficiency of PET during its deployment for clinical purposes, the deployment should take place in close collaboration with university hospital centres and university institutes.

ACKNOWLEDGMENTS

This report was prepared at the request of the *Agence d'évaluation des technologies et des modes d'intervention en santé* (*AÉTMIS*) by **François-Pierre Dussault, Ph.D.,** molecular biologist and biochemist, **Van H. Nguyen**, pharmacist and health economist, and **Dr. Fatiha Rachet**, cardiologist, all three consulting researchers for the Agency. The continuous collaboration of **Jean-Marie Lance**, health economist and the Agency's scientific director, helped improve the quality of this report. The Agency wishes to thank all of these individuals and calls special attention to Dr. Dussault's coordinating role in this project.

The Agency thanks the members of the Positron Emission Tomography Advisory Committee for having discussed the topic and read and commented on the different versions of the working documents during the committee's five meetings. The Agency is especially grateful to the committee's chairman, **Dr. Jean-Marie Moutquin**, obstetrician and gynecologist and scientific director of the Centre hospitalier universitaire de Sherbrooke's Clinical Research Centre and a member of *AÉTMIS's* board of directors, for his availability and his active contribution to the realization of this project.

• **François Bénard**	Nuclear Physician and Medical Director—PET, Centre hospitalier universitaire de Sherbrooke (CHUS), Sherbrooke
• **Peter Bogaty**	Cardiologist, Institut universitaire de cardiologie, Hôpital Laval, Sainte-Foy
• **James Brophy**	Cardiologist, Centre hospitalier de l'Université de Montréal - Notre-Dame Branch, Montréal
• **Raymond Carrier**	Biophysicist and Assistant Director, Technological Resources, Centre hospitalier de l'Université de Montréal
• **Carolyn R. Freeman**	Radio-oncologist, McGill University Health Centre, Montréal
• **James A. Hanley**	Statistician, Department of Epidemiology and Biostatistics, McGill University, Montréal
• **Yves Lacasse**	Pneumologist, Hôpital Laval, Sainte-Foy
• **Jacques Laplante**	Hemato-oncologist, Hôpital du Sacré-Cœur, Montréal
• **Jacques Lévesque**	Radiologist, Chief of Medical Imaging, Centre hospitalier universitaire de Québec, Québec
• **Serge Péloquin**	Medical biologist, Department of Technology Development and Assessment, Division of Medical and University Affairs, Ministère de la Santé et des Services sociaux, Québec City

The Agency especially wishes thank those committee members who made an additional contribution to this report. They are **Dr. François Bénard,** for the sections on the technical aspects and costs of PET; **James A. Hanley, Ph.D.**, for the sections dealing with the methodological aspects of assessing diagnostic tests and part of the update in the field of oncology; **Drs. Peter Bogaty** and **Yves Lacasse**, for their part in constructing the economic models; and **Serge Péloquin**, for having made it easier to obtain Québec statistics on certain imaging devices and detailed information on certain diagnosis-related groups (APR-DRGs) for cost estimate purposes.

105-06920/

The Agency also thanks **Renald Lemieux**, medical physicist and head of radiation protection in the Department of Radiobiology, Centre hospitalier universitaire de Sherbrooke, for writing the appendix on radiation protection, and **Daniel Blay** and **Janet M. Faith,** research assistants affiliated with McGill University, for their contribution to the oncology and neurology updates.

The Agency also expresses its gratitude toward different members of its research and support staff and other, contractual resources who were involved in preparing this report: **Pierre Vincent**, librarian, and **Micheline Paquin**, library technician, for their unceasing support in identifying (retrospective search and bimonthly profiles) and obtaining documentation; and **Karina Lapierre**, for her unflagging contribution during every stage of the preparation of this report, from extracting comparative information on the positions of different organizations to doing the oncology and neurology updates and the French adaptation of these updates and of other sections of this report, collating the different manuscripts, preparing the progress reports and formatting the final version of the report. Lastly, the Agency wishes to thank Mark Wickens, translator, for this English version of the report.

TABLE OF CONTENTS

SUMMARY I
ACKNOWLEDGMENTS V
TABLE OF CONTENTS VII
LIST OF TABLES AND FIGURES X
ABBREVIATIONS, INITIALISMS AND ACRONYMS XIII
GLOSSARY XVII
1. INTRODUCTION 1
  1.1 CONTEXT 1
  1.2 THE REQUESTS THAT GAVE RISE TO THIS REPORT 1
  1.3 INTERNAL AND EXTERNAL COLLABORATION 2
2. POSITION EMISSION TOMOGRAPHY (PET) 5
  2.1 GENERAL DESCRIPTION 5
  2.2 DISTRIBUTION OF PET 5
3. OBJECTIVES AND METHODOLOGICAL STRATEGIES 7
  3.1 OBJECTIVES 7
  3.2 IDENTIFICATION, SELECTION AND EVALUATION OF DATA 7
    3.2.1 Results of literature searches 7
    3.2.2 Assessment reports 8
    3.2.3 Modification of the methodological quality scale 11
    3.2.4 Assessment strategy chosen by *AÉTMIS* 12
4. CLINICAL USES OF PET 13
  4.1 ONCOLOGY 14
    4.1.1 Lung cancer 14
    4.1.2 Colorectal cancer 18
    4.1.3 Melanoma 21
    4.1.4 Head and neck cancer 25
    4.1.5 Lymphoma 28
    4.1.6 Breast cancer 30
    4.1.7 Prostate cancer 32
    4.1.8 Other cancers 33
    4.1.9 Review of the positions published before or in 2000 (oncology) 33
  4.2 NEUROLOGY 34
    4.2.1 Dementia and Alzheimer's disease 34
    4.2.2 Refractory epilepsy 35
    4.2.3 Brain tumors (mainly glioma) 38
    4.2.4 Other clinical uses in neurology and psychiatry 41
    4.2.5 Review of positions published in or before 2000 (neurology) 42
  4.3 CARDIOLOGY 42
    4.3.1 General data 42
    4.3.2 The role of PET in cardiology 43
    4.3.3 Previous positions and update 46
    4.3.5 The role of PET among the currently used nuclear medicine tests 50
    4.3.6 Conclusion 51
  4.4 ECONOMIC CONSIDERATIONS 52
    4.4.1 Australian assessment (MSAC) 52
    4.4.2 1999-2000 update - Economic aspects 52
    4.4.3 Study specific to Québec: non-small-cell lung cancer (NSCLC) 54
    4.4.4 Study of myocardial viability in the Québec context: An exploratory analysis of the potential impact 60

4.4.5 Studies concerning other uses in oncology and neurology 64
4.5 GRADING CLINICAL USES 64
4.5.1 Recognized clinical uses 64
4.5.2 Potential clinical uses 65
4.5.3 Unrecognized clinical uses 65

5. DISCUSSION 67
5.1. ASSESSMENT OBJECTIVES AND STRATEGY 67
5.2 ECONOMIC CONSIDERATIONS 68
5.3 LIMITATIONS OF THE ASSESSMENT 69

6. SUGGESTIONS FOR DEPLOYING PET IN QUÉBEC 71
6.1 CLINICAL NEEDS 71
6.2 PHYSICAL AND HUMAN RESOURCES REQUIRED FOR PET 71

7. CONCLUSIONS AND RECOMMENDATIONS 75
7.1 CONCLUSIONS 75
7.2 RECOMMENDATIONS 76

APPENDIX 1: TECHNICAL DATA ON PET 79
A1.1 EQUIPMENT FOR PRODUCING POSITRON-EMITTING RADIOISOTOPES 79
A1.1.1 Shielded conventional nuclear medicine camera equipped with a high-energy collimator (511 keV) 81
A1.1.2 Collimator-less hybrid nuclear medicine camera for detecting coincidence photons 81
A1.1.3 Dedicated PET instruments 82
A1.2 SAFETY 83
A1.3 PRE-PET SCAN PATIENT PREPARATION 83
A1.3.1 Oncology studies 83
A1.3.2 Brain studies 84
A1.3.3 Cardiac studies 84
A1.4 ROUTINE CLINICAL PROCEDURES USED DURING PET SCANNING 84
A1.4.1 Oncology studies 84
A1.4.2 Brain studies 84
A1.4.3 Cardiac studies 85
A1.4.4 Glucose metabolism studies 85

APPENDIX 2: RADIATION PROTECTION IN THE POSITRON EMISSION TOMOGRAPHY (PET) LABORATORY 89
A2.1 INTRODUCTION 89
A2.2 REQUIRED LICENSES 90
A2.3 THE PERSONNEL REQUIRED 90
A2.4 PACKAGING FOR THE RADIOISOTOPE 91
A2.5 RADIOISOTOPE DISTRIBUTION DOCUMENTS 92
A2.6 PROCEDURE FOR PREPARING RADIOACTIVE PACKAGES 92
A2.7 THE CARRIER 93
A2.8 EMERGENCY PROCEDURE 93
A2.8.1 General emergency procedure 93
A2.8.2 Procedure carried out by a specialized carrier 94
A2.9 LEVELS OF RESPONSIBILITY 94

APPENDIX 3: GEOGRAPHIC DISTRIBUTION OF PET CENTRES 97

APPENDIX 4: LOCATION OF IMAGING EQUIPMENT (OTHER THAN PET EQUIPMENT) 103

APPENDIX 5: DESCRIPTION OF ASSESSMENT REPORTS 109
A5.1 COUNCIL OF MEDICAL IMAGING 109
A5.2 MINNESOTA HEALTH TECHNOLOGY ADVISORY COMMITTEE 109
A5.3 MANAGEMENT DECISION AND RESEARCH CENTER, DEPARTMENT OF VETERANS AFFAIRS -TECHNOLOGY ASSESSMENT PROGRAM (VA-TAP) 109

A5.4 International Network of Agencies for Health Technology Assessment ... 109
A5.5 Blue Cross Blue Shield Association Technology Evaluation Center ... 110
A5.6 Medicare Services Advisory Committee (Australia) ... 110
A5.7 Health Care Financing Administration (United states) ... 110
A5.8 Comité d'Évaluation et de Diffusion des Innovations Technologiques (CÉDIT) ... 111
A5.9 National Health Services - Research & Development (United Kingdom) ... 111
A5.10 Andalusia Health Technology Assessment Agency (AHTAA) ... 112

APPENDIX 6: SEARCH, SELECTION AND EVALUATION OF STUDIES ... 115
A6.1 Search ... 115
A6.2 Selection ... 116
A6.3 Evaluation of diagnostic tests ... 116

APPENDIX 7: POSITIONS OF CURRENT AND POTENTIAL USERS, ASSESSMENT AGENCIES AND REIMBURSEMENT ORGANIZATIONS ACCORDING TO THE CLINICAL USE OF PET ... 123
A7.1 Oncology ... 124
  A7.1.1 Lung cancer ... 124
  A7.1.2 Colorectal cancer ... 127
  A7.1.3 Melanoma ... 129
  A7.1.4 Head and neck cancer ... 130
  A7.1.5 Lymphoma ... 133
  A7.1.6 Breast cancer ... 134
  A7.1.7 Prostate cancer ... 135
A7.2 Neurology ... 137
  A7.2.1 Dementia and Alzheimer's disease ... 137
  A7.2.2 Refractory epilepsy ... 138
  A7.2.3 Brain tumors (glioma) ... 140
A7.3 Cardiology ... 142

APPENDIX 8: SELECTED STUDIES ON PET ... 149
A8.1 Lung cancer ... 149
A8.2 Colorectal cancer ... 156
A8.3 Melanoma ... 159
A8.4 Head and neck cancer ... 163
A8.5 Lymphoma ... 167
A8.6 Breast cancer ... 169
A8.7 Prostate cancer ... 171
A8.8 Miscellaneous uses (not examined in this report) ... 172
A8.9 Alzheimer's disease ... 175
A8.10 Refractory epilepsy ... 175
A8.11 Brain tumors (mainly glioma) ... 178
A8.12 Myocardial viability ... 184

APPENDIX 9: METHODOLOGICAL QUALITY OF STUDIES ... 191

APPENDIX 10: PET COST COMPONENTS ... 205

APPENDIX 11: ECONOMIC MODELS: ADDITIONAL INFORMATION ... 211

APPENDIX 12: LIST OF EXPERTS CONSULTED FOR THE PURPOSE OF CREATING THE DECISION TREES ... 223

REFERENCES ... 227

LIST OF TABLES AND FIGURES

TABLES

TABLE 1: CLASSIFICATION OF THE POSITIONS OF ASSESSMENT ORGANIZATIONS AND AGENCIES 14
TABLE 2: RADIOPHARMACEUTICAL TRACERS USED MOST OFTEN FOR PET IN CARDIOLOGY 43
TABLE 3: LITERATURE REVIEW ON THE COST-EFFECTIVENESS OF PET IN LUNG CANCER 52
TABLE 4: LIST OF THE VARIABLES USED IN THE LUNG CANCER MODEL 56
TABLE 5: RESULTS FOR EACH STRATEGY PER PATIENT (LUNG CANCER) 58
TABLE 6: LIST OF THE VARIABLES USED IN THE MYOCARDIAL VIABILITY MODEL 62
TABLE 7: RESULTS OF THE ECONOMIC ANALYSIS FOR MYOCARDIAL VIABILITY 62
TABLE 8: CYCLOTRONS PRODUCTS 89
TABLE 9: NUCLEAR REACTIONS FOR PRODUCING RADIOISOTOPES 89
TABLE 10: RADIOISOTOPE PRODUCTION PARAMETERS 90
TABLE 11: GEOGRAPHIC DISTRIBUTION OF PET CENTRES 97
TABLE 12: CLINICAL USE OF PET AT CHUS 98
TABLE 13: NUMBER OF CLINICAL SCANS AND WAITING TIMES AT CHUS 98
TABLE 14: SOURCE OF PATIENTS AT CHUS 98
TABLE 15: EQUIPMENT OTHER THAN PET EQUIPMENT BY REGION (QUÉBEC) 103
TABLE 16: IMAGING EQUIPMENT IN QUÉBEC 104
TABLE 17: STUDY SELECTION CRITERIA (INCLUSION AND EXCLUSION) 116
TABLE 18: METHODOLOGICAL QUALITY OF DIAGNOSTIC ACCURACY AND DIAGNOSTIC THINKING EFFICACY STUDIES 118
TABLE 19: ASSESSING THE QUALITY OF INDIVIDUAL STUDIES:CLASSIFICATIONS OF STUDY DESIGNS AND LEVELS OF EVIDENCE 119
TABLE 20: POSITIONS – LUNG CANCER 124
TABLE 21: POSITIONS – COLORECTAL CANCER 127
TABLE 22: POSITIONS - MELANOMA 129
TABLE 23: POSITIONS - HEAD AND NECK CANCER 131
TABLE 24: POSITIONS - LYMPHOMA 133
TABLE 25: POSITIONS – BREAST CANCER 134
TABLE 26: POSITIONS – PROSTATE CANCER 135
TABLE 27: POSITIONS – DEMENTIA AND ALZHEIMER'S DISEASE 137
TABLE 28: POSITIONS – REFRACTORY EPILEPSY 138
TABLE 29: POSITIONS – NEURO-ONCOLOGY (BRAIN TUMORS, MAINLY GLIOMA) 140
TABLE 30: POSITIONS - CARDIOLOGY 142
TABLE 31: SELECTED STUDIES ON PET (ONCOLOGY) 149
TABLE 32: SELECTION OF STUDIES ON PET (NEUROLOGY) 175

TABLE 33: SELECTION OF STUDIES USING A CLINICAL CRITERION AS AN ASSESSMENT CRITERION AND STUDIES ON CHANGES IN MANAGEMENT DUE TO PET SCAN RESULTS (CARDIOLOGY) 184
TABLE 34: SELECTION OF STUDIES OF THE USE OF PET, USING AN INTERMEDIATE CRITERION AS AN ASSESSMENT CRITERION (CARDIOLOGY: FUNCTIONAL REVERSIBILTY OF SEGMENTAL WALL MOTION) 186
TABLE 35: METHODOLOGICAL QUALITY OF STUDIES – LUNG CANCER 191
TABLE 36: METHODOLOGICAL QUALITY OF STUDIES – COLORECTAL CANCER 194
TABLE 37: METHODOLOGICAL QUALITY OF STUDIES - MELANOMA 194
TABLE 38: METHODOLOGICAL QUALITY OF STUDIES – HEAD AND NECK CANCER 196
TABLE 39: METHODOLOGICAL QUALITY OF STUDIES – LYMPHOMA 197
TABLE 40: METHODOLOGICAL QUALITY OF STUDIES – BREAST CANCER 199
TABLE 41: METHODOLOGICAL QUALITY OF STUDIES – PROSTATE CANCER 199
TABLE 42: METHODOLOGICAL QUALITY OF STUDIES – OTHER APPLICATIONS(NOT EXAMINED IN THIS REPORT) 200
TABLE 43: METHODOLOGICAL QUALITY OF STUDIES – NEUROLOGY 201
TABLE 44: PURCHASE PRICES (CYCLOTRON + PET) 205
TABLE 45: PURCHASE PRICES (PET WITHOUT CYCLOTRON) 205
TABLE 46: OPERATING COSTS (CYCLOTRON + PET) 206
TABLE 47: OPERATING COSTS (PET WITHOUT CYCLOTRON) 207
TABLE 48: VARIABLES, INTERVALS AND PREDEFINED DISTRIBUTIONS FOR THE MONTE CARLO ANALYSIS (LUNG CANCER) 214
TABLE 49: UNIVARIATE SENSITIVITY ANALYSIS (LUNG CANCER) 215
TABLE 50: MONTE CARLO ANALYSIS (LUNG CANCER): MEAN, MEDIAN AND QUARTILES 216
TABLE 51: DISTRIBUTION OF INCREMENTAL COST-EFFECTIVENESS RATIOS FOR THE 1,000 MONTE CARLO SIMULATIONS (LUNG CANCER) 217
TABLE 52: LIST OF VARIABLES AND PREDEFINED DISTRIBUTIONS (MYOCARDIAL VIABILITY) 219

FIGURES

FIGURE 1: CATEGORIES OF RADIOACTIVITY 91
FIGURE 2: HAZARDOUS MATERIALS BILL OF LADING (SPECIMEN) 93
FIGURE 3: GROWTH IN THE DEMAND FOR PET AT CHUS (SHERBROOKE) 99
FIGURE 4: DECISION TREE (LUNG CANCER) 211
FIGURE 5: MONTE CARLO ANALYSIS: 1,000 SIMULATIONS (LUNG CANCER) 216
FIGURE 6: DECISION TREE (MYOCARDIAL VIABILITY) 218
FIGURE 7: MONTE CARLO ANALYSIS: 1,000 SIMULATIONS, DETECTION OF MYOCARDIAL VIABILITY 219

ABBREVIATIONS, INITIALISMS AND ACRONYMS

ACRIN	American College of Radiology Imaging Network
AÉTMIS	Agence d'évaluation des technologies et des modes d'intervention en santé du Québec
AHFMR	Alberta Heritage Foundation for Medical Research
AHRQ	Agency for Health Research and Quality (USA)
AHSSS	An Act respecting health services and social services (Québec)
AHTAA	Andalusia Health Technology Assessment Agency
AMSMNQ	Association des médecins spécialistes en médecine nucléaire du Québec
AP-HP	Assistance publique - Hôpitaux de Paris
APR-DRG	All patients revised - diagnostic related groups
ARQ	Association des radiologistes du Québec
ASCO	American Society of Clinical Oncology
ASR	Age-, sex- and race-adjusted annual mortality rate (general population)
BCBSA	Blue Cross Blue Shield Association (USA)
BCBSA-TEC	Blue Cross Blue Shield Association - Technology Evaluation Centre (USA)
BGO	Bismuth germanium oxide
CAHTA	Catalan Agency for Health Technology Assessment
CEA	Carcinoembryonic antigen
CÉDIT	Comité d'Évaluation et de Diffusion des Innovations Technologiques (France)
CHUM	Centre hospitalier de l'Université de Montréal
CHUQ	Centre hospitalier universitaire de Québec
CHUS	Centre hospitalier universitaire de Sherbrooke
CI	Confidence interval
CMI	Council of Medical Imaging (Ontario)
CMS	Centers for Medicare and Medicaid Services (new name for the HCFA)
CNS	Central nervous system
CNSC	Canadian Nuclear Safety Commission
CQLC	Conseil québécois de lutte contre le cancer
CRC	Centre de recherche clinique (Sherbrooke)
CT	Computerized tomography
DEALE	Declining exponential approximation of life expectancy
DHAC-DTB	Department of Health & Aged Care - Diagnostics & Technology Branch (Australia)

DSR	Disease-related survival rate
ECRI	Emergency Care and Research Institute (USA)
EEG	Electroencephalography or electroencephalogram
ENT	Ears, nose and throat
EPC	Evidence-based Practice Centre (USA)
EUS	Endoscopic ultrasound
FDA	Food and Drug Administration (USA)
FDG	Fluorodeoxyglucose
FMSQ	Fédération des médecins spécialistes du Québec
GSO	Gadolinium oxyorthosilicate
HCFA	Health Care Financing Administration (USA) – now called the Centers for Medicare and Medicaid Services (CMS)
ICES	Institute of Clinical Evaluative Sciences (Ontario)
INAHTA	International Network of Agencies for Health Technology Assessment (network whose secretariat is in Sweden)
ITC	Interterritorial Council (of the national health-care system of Andalusia)
keV	Kiloelectron volt
LSO	Lutetium oxyorthosilicate
LV	Left ventricle
LVEF	Left ventricular ejection fraction
MBq	Megabecquerel
MBS	Medicare Benefit Schedule (USA)
MET	Methionine
MHTAC	Minnesota Health Technology Advisory Committee
MNI	Montreal Neurological Institute
MR	Magnetic resonance
MRI	Magnetic resonance imaging
MSAC	Medicare Services Advisory Committee (Australia)
MSSS	Ministère de la Santé et des Services sociaux (Québec)
NaI	Sodium iodide
NCIC	National Cancer Institute of Canada
NHL	Non-Hodgkin's lymphoma
NHS R&D	National Health Services Research & Development (United Kingdom)
NPV	Negative predictive value
NSCLC	Non-small-cell lung cancer
PET	Positron emission tomography
PPV	Positive predictive value
PSA	Prostate-specific antigen

PTC	Positron Technology Committee (Fédération des médecins spécialistes du Québec)
PV-	Negative predictive value
PV+	Positive predictive value
RAMQ	Régie de l'assurance-maladie du Québec
ROC	Receiver operating characteristics
ROI	Region of interest
R.S.Q.	Revised Statutes of Québec
SCLC	Small-cell lung cancer
SD	Standard deviation
SPECT	Single-photon emission computed tomography
SPN	Solitary pulmonary nodule
STARD	Standard for Reporting of Diagnostic Accuracy
SUV	Standardized uptake value
T/B	Tumor-to-background ratio
TFNAB	Transthoracic fine-needle aspiration biopsy
TRUS	Transrectal ultrasound
USP-DI	*United States Drug Pharmacopeia - Drug Information*
VA-TAP	Veterans Affairs - Technology Assessment Program (USA)

GLOSSARY

Coincidence detection	Characteristic of PET technology based on the simultaneous detection of photons at the opposite poles of a detector.
Computed tomography	A radiologic examination consisting in reconstructing 2- or 3-D images from one-dimensional projections from several angles.
Conventional imaging	A medical imaging technology that permits only the anatomical localizaton of lesions, such as radiography, computed axial tomography, ultrasonography, magnetic resonance imaging and scintigraphy.
Half-life	The amount of time it takes a radioactive substance to lose half of its radioactivity, that is, half of its number of radioactive atoms.
Isotope	One of two or more types of atoms of a given element whose nucleus contains the same number of protons but a different number of neutrons.
Magnetic resonance imaging	An imaging technique that exploits the orientation properties of the magnetic moment of hydrogen nuclei in the human body under the effect of a strong magnetic field.
Metabolic imaging	Visualization of biochemical changes or reactions in the body.
Morphological imaging	Visualization of the shape and structure of organs and tissues.
Positron	A subatomic particle whose mass is equal to that of an electron but which is oppositely charged, i.e., positive.
Radioisotope	An unstable isotope of an element that breaks up or disintegrates spontaneously, emitting radiation and moving to a more stable state in the process.

Radiopharmaceutical	A radionuclide-labelled pharmaceutical or chemical preparation used for diagnostic or therapeutic purposes.
Radiotracer	A radionuclide or radiolabelled chemical used to reveal the path travelled by nonradioactive substances or their location.
Scintigraphy	A medical imaging technique for showing both the structure and functioning of organs and of certain pathological processes. The detection of the radiation emitted by a radioactive substance introduced into the body that has a particular affinity for a given organ or tissue.
Scintillator	A substance that emits visible light when hit by a subatomic particle or an x-ray or a gamma ray.
Signal amplification and processing electronics	Conversion of an optical image into an electronic image in order to increase the luminosity and accuracy of a radiological image.
Single-photon emission tomography	(SPECT) A medical imaging technique based on detecting, by means of a special camera, radiation emitted by a radioactive substance introduced into the body (scintigraphy) and which provides cross-sectional images (tomography) of different organs.
Standardized uptake value (SUV)	Activity of a tracer (counts/pixel/second) in the regions of interest (ROIs)/injected dose of tracer + patient's body mass index (mCi/kg).
Ultrasound	(or **ultrasonography**). Technique for visualizing certain internal organs by studying the reflection of a beam of ultrasounds.

1. INTRODUCTION

1.1 CONTEXT

Introduced in the mid-70s, positron emission tomography (PET) has prompted a great deal of research because of its ability to analyze the metabolic activity and pathophysiology of tissues. For the most part, the other medical imaging technologies (referred to as "conventional") only permit the anatomical localization of lesions (radiography, computed axial tomography, ultrasonography, magnetic resonance imaging, etc.). Over the past decade, the clinical use of PET for diagnostic and therapeutic guidance and monitoring purposes has increased dramatically, as evidenced in the United States by the ever-increasing list of applications covered by public and private health insurance plans.

In Canada, current and potential PET users enthusiastically recommend the deployment of this technology for clinical purposes. In Québec, there are presently two PET centres, each equipped with scanners and a cyclotron, which is helping to fuel this trend.

Contrary to this enthusiasm, the conclusions of most of the assessment organizations that have examined this matter—and this, still quite recently—contain a number of provisos on the clinical use of PET. These reservations stem mainly from the paucity of adequate studies of the efficacy and cost-effectiveness of PET in relation to the existing medical imaging technologies.

It was in this context that the *Agence d'évaluation des technologies et des modes d'intervention en santé (AÉTMIS)* began, in late September 2000, to examine positron emission technology in Québec. In this report, we first explain the origin of the requests to have this technology assessed by *AÉTMIS* and the steps undertaken to meet these requests. This is followed by a description of the technology, the positions of the current and potential users of PET, those of third-party payers and assessment agencies, and an update on publications that postdate the latest assessments. The current and foreseeable uses are listed before discussing the avenues for the possible deployment of this technology for clinical purposes in Québec.

1.2 THE REQUESTS THAT GAVE RISE TO THIS REPORT

In 1999, the management of the Office of Professional Development and Health Policy of the Fédération des médecins spécialistes du Québec (FMSQ) set up a committee on positron technology (PTC).

The committee's mandate was to assess, within the framework of the expertise of the specialties represented on the committee and from a report submitted, in May 2000, to the FMSQ by the Association des médecins spécialistes en médecine nucléaire du Québec (AMSMNQ), the scientific and clinical value of positron emission tomography imaging technology and the advisability of recommending its use in Québec, but without specifying, at this point, any sites for implementation.

The specialties represented on the working committee were as follows: cardiology, general surgery, hemato-oncology, nuclear medicine, neurosurgery, neurology, respirology, psychiatry, radiology and radio-oncology. A representative from the Ministère de la Santé et des

Services sociaux (MSSS) also sat on this committee, as an observer. In September 2000, several of the committee's members submitted, as private individuals or as representatives of their respective specialties, a report on the potential use of PET.

Concurrently with these activities, given the increasing number of potential uses of PET in oncology, the Conseil québécois de lutte contre le cancer (CQLC) was taking an active interest in this technology.

The FMSQ and the CQLC contacted *AÉTMIS* in September 2000 for the purpose of initiating a collaborative effort between the three organizations with a view to drafting an assessment report on PET. On the basis of this assessment, it would be possible to make recommendations concerning the deployment of this technology.

During a meeting held on September 26, 2000, which was attended by members of the FMSQ's Positron Technology Committee and representatives from *AÉTMIS*, it was agreed that the process of evaluating the hard data and drafting a report would involve interaction between the authors at *AÉTMIS* and an advisory committee consisting of specialists from the FMSQ and representatives from organizations interested in preparing this report, namely, the CQLC and the MSSS.

The advisory committee's main function was to assist in the drafting of the *AÉTMIS* report by helping to incorporate the existing data on the clinical use of PET and the results of the evaluations of these data by various organizations. The members of the advisory committee are mentioned in the Acknowledgments. *AÉTMIS* invited one of the members of its board of directors, Dr. Jean-Marie Moutquin, to chair the committee.

1.3 INTERNAL AND EXTERNAL COLLABORATION

Because of the wide array of current and potential uses of PET and of a tight deadline for preparing a final report, *AÉTMIS* sought internal and external collaboration to take advantage of specialized expertise and to document the various aspects to be covered. The in-house team consisted of François-Pierre Dussault, Ph.D., who wrote the entire report, except for the sections on cardiology, which were prepared by Dr. Fatiha Rachet, and the section on economics, which was written by Van H. Nguyen. These three authors revised the entire report at the different stages of its preparation. Other writers contributed as well. They are listed below.

Specific contributions were requested from members of the advisory committee or other experts. Thus, James Hanley, Ph.D., collaborated in developing the methodological selection-and-assessment strategy; Dr. François Bénard wrote the parts on technical data, PET-related activities at CHUS and data interpretation; and Renald Lemieux wrote the section on radiation protection. Two external resource persons were asked to select, retrieve and evaluate recent publications in the field of oncology (Janet Faith and Daniel Blay), which had been previously identified, located and acquired by *AÉTMIS's* documentation staff (Pierre Vincent and Micheline Paquet).

Furthermore, a willingness on the part of *AÉTMIS* and Ontario's Institute of Clinical Evaluative Sciences (ICES), both of which were assessing this technology for their respective provinces, to cooperate led to exchanges of information on each other's methodological process, for the purpose of drafting independent reports. A meeting aimed at comparing results, obtained or anticipated, took place, and a framework for a joint statement on these two agencies' positions regarding the clinical use of this technology was developed. ICES had begun its work much earlier than *AÉTMIS* and published its report in May 2001. It is available on the Web at http://www.ices.on.ca. Both agencies' conclusions call for guided deployment of PET for clinical purposes.

While this report was being drafted, there were informal exchanges with other assessment agencies, especially the Comité d'évaluation et de diffusion des innovations technologiques (CÉDIT). Once again, although there was no joint drafting, these exchanges provided an opportunity to compare methodological approaches and goals, thus preparing the groundwork for future collaboration.

2. POSITION EMISSION TOMOGRAPHY (PET)

2.1 GENERAL DESCRIPTION

PET is a 3-dimensional medical imaging technology. Images are obtained by administering radiopharmaceuticals containing positron-emitting tracers. Positrons are particles whose mass is equivalent to that of electrons but which are oppositely charged. "Positron" is a blend of "positive" and "electron".

Positrons leave the nuclei of isotopes and pair off with electrons after travelling a few millimetres to form short-lived positroniums, which annihilate, emitting two 511-keV photons oriented in opposite directions (180°). The simultaneous detection of these photons by appropriately aligned detectors is used, after computer processing, to constitute a 3-dimensional image of the sites of this energy release.

Positrons were discovered some 60 years ago, but the use of their properties for medical imaging purposes did not really begin until about the mid-70s [Phelps et al., 1976]. Intensive research in various areas of application gradually evolved to the clinical use of PET in neurology and cardiology, then in oncology.

The brief overview provided below of the operating principles of PET is supplemented in Appendix 1 with additional details on the equipment (cyclotrons and scanners [Section A1.1]). The appendix also explains the basis of the general opinion regarding the safety of PET (Section A1.2). Another section (A1.3) in this appendix deals with patient preparation, yet another (A1.4) with the examination procedure. The guiding principles and the regulations governing radiation protection, in particular, the transport of positron-emitting isotopes, are detailed in Appendix 2.

Basically, PET is based on identifying, in the body, sites where there is an accumulation of positron-emitting isotopes. These radioisotopes reveal their presence by emitting photons when they enter a stable energy state. One can thus locate isotopes incorporated into molecules that are analogs of natural substrates or that have pharmacologic properties and follow their distribution and accumulation in the body.

The use of fluorine-18 (^{18}F) as a substitute for an oxygen atom in a glucose molecule, for example, permits localization of regions where the accumulation of this analog is indicative of increased glucose metabolism in the tissues [Phelps, 2000]. In effect, the ^{18}F-labelled analog enters cells but is not subsequently metabolized. This feature of PET makes this an attractive technology because, depending on the isotopes used, simple administration by inhalation or intravenous injection enables one to locate an anatomical entity and to simultaneously assess its functional status. This distinguishes PET from a good number of imaging techniques that provide information mainly on the anatomical location of the sites of interest, although some of these techniques can provide functional information.

2.2 DISTRIBUTION OF PET

The increase in the number of PET centres worldwide has occurred rapidly, especially over the past few years. In Germany, there were six PET centres in 1988. In October 1999, there were 65. In the United States, there were about 55 centres in 1997, with the figure exceeding 300 in February 2000. Nonetheless, the implementation of PET is not uniform from continent to continent or country to country, as can be seen from Table 11 in Appendix 3. This table does not make a distinction between the uses of PET for clinical purposes and those for research purposes. However, PET already seems to have become commonplace at about a hundred centres worldwide and is a research technology used at a hundred or so others, and a large number of potential users would like to acquire it.

It is in oncology that most PET scans are covered, accounting for 65% of all payments. Based on the results of an INAHTA survey, about 85% of clinical PET scans reimbursed worldwide were performed in Australia, Switzerland, Denmark and the United States. The United States, Switzerland and Denmark reimburse the largest number of PET scans per 100,000 patients [Adams et al., 1999].

The uses of PET in neurology account for 25% of the clinical PET scans that are reimbursed. The health-care systems in Switzerland, Australia and Finland are those that reimburse the largest number of PET scans in neurology. The INAHTA survey revealed that the number of scans in each area of use varies considerably. For instance, scans for brain tumors and epilepsy account for 75% of all PET scans in neurology [Adams et al., 1999].

The uses of PET in cardiology account for the smallest proportion (6%) of PET scans reimbursed worldwide, and 60% of them are performed to detect viable myocardium. Fewer than half of the public health-care systems that participated in the INAHTA survey cover the use of PET in cardiology, the largest proportion of PET cardiac studies being performed in the United States, Switzerland and Denmark [Adams et al., 1999].

In Canada, there are PET scanners in seven cities located in four provinces. In Québec, there are two centres equipped with cyclotrons and scanners, both research-oriented and clinically oriented in different proportions.

The Montreal Neurological Institute (MNI) has, for about 10 years, been using PET to conduct research on multifocal epilepsy, recurrent brain tumors, Parkinson's disease and Alzheimer's disease. The clinical use of PET at the institute is limited to about a hundred patients a year.

The PET unit at the Centre hospitalier universitaire de Sherbrooke (CHUS) began operation in 1998 and uses PET for research and clinical purposes. Between May 15, 2000 and May 15, 2001, 1,253 clinical scans were performed. Scans in oncology patients (lung cancer, lymphoma, etc.) topped the list, as can be seen from Table 12 in Appendix 3. Table 14 shows where the patients were from, and Table 13 indicates that the average waiting time is 45 days. Figure 3 in that appendix shows the increase in demand over the past year. It went from about 60 a month in 1999 to about 100 in 2000 and continues to increase.

It should be noted that the breakdown of these scans reflects the centre's activities and can therefore not be used immediately to extrapolate to all of Québec's needs.

3. OBJECTIVES AND METHODOLOGICAL STRATEGIES

3.1 OBJECTIVES

The objectives of *AÉTMIS's* assessment are:

1. To gather hard data on the clinical use of PET in different fields, in particular, oncology, neurology and cardiology; and
2. To make recommendations concerning the possible deployment of PET in Québec.

The methodological strategy for the first objective is the subject of the present chapter. The second objective is discussed in light of the conclusions regarding the clinical efficacy and cost-effectiveness of PET (Chapter 4) and the prerequisites for implementing this technology (Chapter 6).

3.2 IDENTIFICATION, SELECTION AND EVALUATION OF DATA

The identification of the relevant data involved several steps, most of which were carried out simultaneously. First, the reports stemming from the work of the Positron Technology Committee (PTC) of the Fédération des médecins spécialistes du Québec (FMSQ) were inventoried and consulted (see the section entitled "Reports by current or potential users" in the References). Next, numerous Web sites were searched, and several reports were downloaded (see Appendix 5 for a brief description of the latest ten reports on the subject). Lastly, a protocol for querying bibliographic databases was instituted in October 2000. It included establishing profiles at 2-week intervals and a retrospective search (descriptors listed in Appendix 6). The databases queried were mainly MEDLINE (PubMed) and the Cochrane Library. In addition, a few searches were done in Embase, Cancerlit and in health technology economic assessment databases.

Given that the assessment reports identified are of recent publication (e.g., that of the MSAC in Australia [Ghersi et al., March 2000, official version disseminated in April 2001: http://www.health.gov.au/haf/pet] and the HCFA's report [Tunis et al., December 2000]), it was agreed that the retrospective search would be limited to forming a bridge between the surveys of the latest available reports and recent publications postdating those reports.

To ensure overlapping between the end of the surveys of the recent reports and certain publications predating those reports, given the indexing time in certain databases, such as MEDLINE, the cut-off date for the retrospective search performed in November 2000 was set at January 1999. The surveys of bimonthly profiles began in November 2000 and continued until February 2001.

3.2.1 Results of literature searches

Even though the literature search was limited in time, it generated several thousand individual references. Of these, about 600 were considered for selection, based on the criteria presented below (Section 3.2.3 and Appendix 6). On the whole, the publications identified show that PET is rapidly advancing from a technological standpoint and that its clinical applications are evolving quickly and in a diversified manner.

Thus, we identified highly technical articles on various aspects, such as new crystals for detectors, new attenuation calculations, new markers and, more generally, new-generation devices that increase PET's clinical performance.

We also found numerous results of studies aimed at exploring or validating various applications. In oncology, the objective is mainly to enhance the diagnostic capacity of PET in order to differentiate between benign and malignant lesions, the ability to grade malignant lesions and the ability to assess the spread of the disease in order to guide the choice of treatment, then to measure its results. In neurology, particularly in refractory epilepsy, PET is used to determine the sites of surgical intervention, while in cardiology, it is used to assess myocardial viability in order to optimize the therapeutic options (medical, revascularization or transplantation) and to evaluate coronary perfusion for the diagnosis, prognosis and therapeutic monitoring of coronary patients.

Studies exploring or confirming potential clinical applications of PET are as increasingly numerous in literature searches as comparative studies are sparse, as are economic studies, especially those on the cost-effectiveness of this technology in relation to that of other medical imaging technologies. In this context, the recent assessment reports can shed some light on the clinical performance of PET by providing organized data on this aspect, as will be seen in the following sections.

3.2.2 Assessment reports

PET has been in existence for a few decades now, and its clinical use seems to have been an outgrowth of research. Indeed, structured, exhaustive reports systemically assessing the clinical performance of PET are still recent and few in number. For all practical purposes, the first widely disseminated report was written in 1996, with an update in 1998, by the Veterans Affairs Technology Assessment Program (VA-TAP) [Flynn and Adams, 1996; Adams and Flynn, 1998].

Between these two reports, the problem of evaluating diagnostic tests performed by medical imaging was outlined in a report published by the Department of Veterans Affairs [Adams, 1997] that includes several criteria, which are listed in Appendix 6. These criteria concern the inclusion or exclusion of studies that were identified (Table 17), the evaluation of their methodological quality (Table 18) and the assessment of the overall quality of the results and conclusions (Table 19).

The VA-TAP criteria, which were used to assess the clinical performance of PET, were supplemented with criteria, found in reports from a few other organizations, for evaluating economic studies, which are discussed in Section 4.4.

Since these publications by the VA-TAP, PET has been the subject of reports by assessment agencies and organizations that make recommendations for coverage by public and private health-care systems. Some of these reports were often used as guidelines when drafting the present report (e.g., the report of the Andalusia Health Technology Assessment Agency [AHTAA]; those of the Medicare Services Advisory Committee (MSAC) in Australia; and those of the Blue Cross Blue Shield Association Technology Evaluation Center [BCBSA-TEC] and the Health Care Financing Administration [HCFA] in the United States).

Although the raison d'être of the various organizations concerned with the coverage of clinical examinations and that of assessment agencies are sometimes different, the assessment methodologies used for PET were similar in several cases. Thus, in the United States, the

HCFA turned to the Agency for Health Research and Quality (AHRQ) for evaluating a request for broad PET coverage submitted by a group of promoters of this technology, and the BCBSA submitted questions to its own technology evaluation centre (TEC). For its part, the MSAC, which is an assessment organization, acted on a request from Australia's Minister of Health and Aged Care (MHAC). In short, assessment committees drafted or collaborated closely in the drafting of these organizations' or agencies' conclusions.

Furthermore, these PET assessment reports are closely linked, not only by the criteria used (most of which are those in the VA-TAP report, with slight modifications, depending on the agency or organization), but also by abundant mutual citations. For example, the MSAC refers to the INAHTA, VA-TAP and NHS R&D reports (see Appendix 5 for a brief description of these reports), pointing out that its conclusions are largely consistent with those of those reports. In turn, the HCFA based, in part, its assessment on those of the BCBSA-TEC and the MSAC, in addition to the results of its own study review.

From this standpoint, the MSAC and HCFA reports were a major source of information for this report. That information is described in greater detail below.

3.2.2.1 Report of Australia's Medicare Services Advisory Committee (MSAC)

The MSAC is an independent committee that was set up to advise the Commonwealth Minister for Health and Aged Care on the convincingness of safety, efficacy and cost-effectiveness data on new technologies and new procedures.

There are three main PET centres in Australia. The first one was created in 1992. Gradually, and as the other units were put into operation, the number of main clinical uses increased in oncology (lung cancer, melanoma, gastrointestinal cancer and a few other uses, namely, brain tumors, breast cancer, and head and neck cancer). In cardiology, the number of uses increased until 1994, then decreased.

The issue of PET's diagnostic efficacy quickly arose. In 1993, a 5-year assessment project began at two centres. In 1997, the project was modified to include partial coverage for certain examinations in oncology, neurology and cardiology. Afterwards, other centres put into operation in 1996 and 1998 made a request to receive such coverage.

The evaluation of the merits of coverage was revived. The matter was submitted to the MSAC, and its report on PET was circulated on a limited basis in March 2000 [Ghersi et al., 2000] for consultation before official approval of the interim-coverage recommendations. The latter were ratified by the Department of Health & Aged Care - Diagnostics & Technology Branch (DHAC-DTB) in a report that became available in August 2000 and which was officially published in April 2001 (www.health.gov.au/haf/pet).

As regards methodology, a team of five experienced evaluators systematically reviewed the publications identified between 1966 and February 2000 on the different uses of PET. The literature search was carried out using several bibliographic databases (MEDLINE, the Cochrane Library and its related databases, assessment agency Web sites, health technology economic evaluation databases, etc.).

The selection criteria were the same as those of the VA-TAP and are presented in Table 17 of Appendix 6. The articles chosen were subjected to the following questions [Jaeschke et al., 1994]:

1. Was there an independent, blind comparison with a reference standard?
2. Did the patient sample include an appropriate spectrum of patients to whom the diagnostic test will be applied in clinical practice?
3. Did the results of the test being evaluated influence the decision to perform the reference standard?
4. Were the methods for performing the test described in sufficient detail to permit replication?

The articles were then grouped according to the different uses of PET: diagnostic (staging, spread, recurrence), therapeutic impact (choice of treatment and therapeutic monitoring), patient outcomes and cost-effectiveness.

The application of the said criteria was supplemented by opinions of experts in nuclear medicine, radiology, cancer surgery, neurology and cardiology.

As an illustration, in the MSAC's literature review of the diagnostic use of PET in non-small-cell lung cancer, 42 papers were selected for assessment. A partial breakdown of these articles revealed 14 on the diagnostic accuracy of PET, six of which were included in the VA-TAP report. Three papers compared computed tomography alone and computed tomography followed by PET. Five studies concerned the detection of distant metastases.

It will be noted that the MSAC's conclusions concerning the clinical uses of PET and its recommendations regarding its interim coverage were ratified by the DHAC-DTB. They are summarized in Chapter 4 and are spelled out in greater detail in Appendix 7.

3.2.2.2 Report of the U.S. Health Care Financing Administration (HCFA)

The HCFA is a federal agency responsible for the Medicare and Medicaid programs in the United States. It also administers the Children's Health Insurance program jointly with the Health Resources and Services Administration. During the last few weeks when this report was being drafted, the administration's name was changed to "Centers for Medicare and Medicaid Services" (CMS). The name "HCFA" was nonetheless kept in this report.

Already in 1995, the HCFA agreed to cover PET scans using rubidium-82 for coronary perfusion imaging and the management of coronary patients. In 1998, it agreed to cover PET scans using FDG (FDG-PET) for staging non-small-cell lung cancer (NSCLC) and evaluating solitary pulmonary nodules (SPNs). In 1999, the list was expanded to include the localization of recurrent colorectal cancer in the context of an elevated carcinoembryonic antigen (CEA) level, the staging of lymphoma (in place of gallium imaging) and the preoperative evaluation of recurrent melanoma (in place of gallium imaging).

In July 2000, the HCFA received a request for broad coverage of FDG-PET scans. The article in support of this request was published in May 2001 [Gambhir et al., 2001]. The request was accompanied by 419 articles and abstracts on 22 diseases. Because of the large amount of data submitted, the HCFA requested assistance from the Agency for Health Research and Quality (AHRQ). The AHRQ had the Evidence-based Practice Center (EPC) perform a validation check on the PET submission. The EPC concluded that the request had not been submitted as a standard systematic literature review. It was, instead, a vast fresco of PET uses. Questions were at once raised about the inclusion criteria in the cited studies. The HCFA concluded that systematic reviews separate from the compilations accompanying the request were necessary in order to substantiate a coverage policy in line with its mandates.

The HCFA completed its task using the Blue Cross Blue Shield Association's assessments, those of the Commonwealth Review of Positron Emission Tomography (DHAC-DTB and MSAC), additional analyses of results on lung and esophageal cancer using material from the requester's submission, and a literature search. The HCFA considered other sources of evidence as well, including extensive consultations with clinical experts in oncology, nuclear medicine, cardiology, neurology and other relevant clinical disciplines.

The literature search was performed by the Evidence-based Practice Center (EPC) in MEDLINE and BIOSIS for each of the uses mentioned in the request. For the 10-year period from 1990 to 2000, the EPC identified more than 500 articles, which were selected and reviewed according to criteria adapted from those in the 1997 VA-TAP report (Tables 17, 18 and 19 in Appendix 6).

In November 2000, the Medicare Coverage Advisory Committee (MCAC) established guidelines for evaluating diagnostic tests and focused on the following questions:

1. Is the evidence sufficient for determining if the use of the diagnostic test provides more-accurate diagnostic information?

   Step 1: Assess the quality of the studies of the test's performance.

   Step 2: Evaluate the possibility that the two tests are complementary.

2. If the test improves diagnostic accuracy, is the evidence adequate to conclude that the improved accuracy would lead to better health outcomes?

   Step 1: Calculate the posttest probability of disease.

   Step 2: Evaluate the potential impact on patient management when two tests differ in terms of the posttest probability of disease.

Over and above the initial request, the following diseases were chosen for assessment purposes: lung cancer, colorectal cancer, lymphoma, cancer of the esophagus, melanoma, head and neck cancer, coronary artery disease and epilepsy. The HCFA concluded that the evidence was sufficient to justify adding certain examinations to the Medicare PET coverage policy. However, the quality of the evidence was not consistent with the standards of practice for assessing diagnostic tests. Several of the studies reviewed had serious methodological biases, which made it difficult to draw a firm conclusion as to the benefits of FDG-PET in clinical practice. The HCFA concludes by stating that, when studies of higher quality are available, it would advisable to reconsider the coverage decision concerning PET scans in order to reflect the advancing state of knowledge [HCFA: Tunis et al., 2000].

3.2.3 Modification of the methodological quality scale

In general, all assessment reports raise the problem of assessing diagnostic tests. These issues are discussed in greater detail in Appendix 6. Not all the criteria proposed by the VA-TAP [Adams, 1997] have been used by the organizations and agencies mentioned thus far, because some of the criteria are inapplicable or because of the nature of studies aimed at documenting the efficacy of PET. These criteria are detailed in Tables 17, 18 and 19 in Appendix 6.

The published criteria do not generally seem to explicitly take into account the simultaneous comparison of two test modalities in a given study. It is recognized [Ransohoff and Feinstein, 1978] that patient characteristics can greatly influence the performance of a given diagnostic modality. This notion is implicit in the phrases "broad generalizability to a variety of patients" and "a narrower spectrum of generalizability" presented in the definitions of grades A and B (Table 18, Appendix 6).

For purposes of this report, the comparison criterion was considered explicitly, for the best way to avoid the likelihood of "partial" comparisons is to insist that the same sample of cases be evaluated for each of the modalities being compared. Otherwise, the accuracy of PET could be assessed with an "easy" sample at one facility and the accuracy of conventional imaging assessed in a more "difficult" sample (or vice versa) at another.

Comparative studies were rated A or B when they included all or some of the criteria (Table 18, Appendix 6). Any study that did not include an explicit comparison between competing technologies or between PET used in conjunction with conventional imaging and conventional imaging used alone was rated C or D. However, in some cases, when there is no other useful test, the sensitivity or specificity of PET must be considered in absolute terms.

3.2.4 Assessment strategy chosen by *AÉTMIS*

AÉTMIS chose, as its point of departure, the expectations of clinicians as expressed in narrative reviews, with no explicit methodology for assessing this technology. This group was designated as follows:

- Current or potential users (opinions of specialists, based on their clinical experience and expertise).

Second, *AÉTMIS* used, as a guideline, the conclusions of assessment reports based on protocols that explicitly state criteria for selecting and evaluating studies of the clinical performance of PET. It will be noted that, while the conclusions of these evaluations serve as a springboard for *AÉTMIS's* assessment, the decisions of other organizations regarding the conditions for using PET (eligibility of centres, conditions for coverage, etc.) cannot be immediately transposed to the situation in Québec. This option led to the grouping of these reports under the following headings:

- Assessment agencies (assessments, using an explicit methodology, of the clinical efficacy of PET).
- Public and private reimbursement organizations (assessments of PET, using an explicit methodology, for the purpose of making PET scan coverage decisions).

Third, the VA-TAP's study selection and evaluation protocols were applied to the publications that were identified from 1999 to February 2001 which had not been included in the previously published assessment reports [Adams, 1997], with the addition of the explicit requirement of comparing the technologies being examined, as described above. The ratings given to the articles selected thus reflect the methodological quality of these studies in *AÉTMIS*'s updates (Tables 35 to 43 in Appendix 9) and are based on the criteria in Table 18 in Appendix 6. However, these ratings are not based on the overall study evaluation criteria, since they are usually inapplicable (Table 19, Appendix VI).

4. CLINICAL USES OF PET

Which uses of PET are clinically effective? The answer to this question is provided by epidemiologic data on the diseases of interest (especially for Québec and Canada), on the conventional diagnostic modalities and on the role of PET in each of the uses examined by *AÉTMIS* in oncology, neurology and cardiology.

This order of presentation is not indicative of the relative importance that *AÉTMIS* attaches to these areas of application. Furthermore, based on the INAHTA survey [Adams, 1999], the breakdown of the reimbursements for all the clinical uses was 65% in oncology, 25% in neurology and 6% in cardiology. Oncology is presented first, as in a number of other assessment reports, no doubt to follow their example. Furthermore, data in oncology and neurology are not always mutually exclusive. As a general rule, the uses in oncology concern tumors other than those of the central nervous system, and part of the section on neurology concerns neuro-oncology (brain tumors), hence the close proximity of these two areas of application in the order of presentation, since there is sometimes some overlapping.

The list of uses examined by *AÉTMIS* is based on information from the literature surveys and expectations expressed by current or potential users. Thus, for each use examined, there is a summary table of the positions expressed by assessment organizations and agencies. These tables provide, in a condensed form, the conclusions based on structured assessments and a basis for comparison with the results of the updates (1999 to February 2001), which confirm or invalidate these conclusions.

Detailed compilations of the positions of current and potential users, reimbursement organizations and assessment agencies are presented in Appendix 7 for each use examined. These positions are expressed in condensed form for the purposes of this section and are ranked on a scale of 1 to 6 (see Table 1 on the following page).

Next in order are the bases for the MSAC's and HCFA's conclusions. In accordance with the explanations given in Section 3.2.4, the MSAC's and HCFA's assessments were used as guidelines for recognizing the clinical efficacy of PET in the uses examined here. Failing an assessment by the MSAC or HCFA, the conclusions of other organizations or agencies were taken into account, if necessary. In accordance with the methodological strategy used by *AÉTMIS*, updates aimed at identifying publications subsequent to the assessment reports are compared with the MSAC's and HCFA's conclusions.

As can be seen from Section 4.4, which concerns the economic aspects of PET, there is a paucity of hard data on the cost-effectiveness of the various uses of PET. The cost-effectiveness of the various uses of PET has not yet been determined, except for the characterization of the solitary pulmonary nodule. This is why these data need to be supplemented by models.

The conclusions of the main organizations or agencies, in particular, those of the MSAC, are not definitive and involve many nuances regarding the interpretation of the significance of the existing hard data. Consequently, the overall conclusions (conclusions of agencies and organizations and conclusions of updates) for each clinical use were classified as follows:

- A clinical use is said to be recognized if the hard data are acceptable (in terms of clinical efficacy).

- It is considered potential if the hard data are acceptable but incomplete.
- It is considered nonrecognized if the data are insufficient to a make a decision, if they show that it performs poorly or if there are no data in the literature surveys carried out for this report.

Table 1: Classification of the positions of assessment organizations and agencies

1	✿	Recognized use.
2	✿/✿	Use recognized by some and considered potential by others.
3	✿	Potential use (but further research is required).
4	✿	Debated (use recognized by some, potential or not recognized by others).
5	✿/✿	Use considered potential by some and not supported by the hard data for others.
6	✿	Evidence insufficient to support this use.
7	NM	Not mentioned.

4.1 ONCOLOGY

In oncology, the following uses were examined: lung cancer, colorectal cancer, melanoma, head and neck cancer, Hodgkin's and non-Hodgkin's lymphoma, breast cancer and prostate cancer.

There are probably several important uses of PET that were not examined in this report. It should therefore not be assumed that PET does not play a role in the uses that are not mentioned here. Based on the MSAC's consultations with PET suppliers, the uses examined in its March 2000 report (lung cancer, colorectal cancer, melanoma, glioma, epilepsy and coronary revascularization) account for only 40% of the PET scans performed in clinical settings.

4.1.1 Lung cancer

4.1.1.1 General data

In Canada, the age-standardized incidence rates for lung cancer have been estimated at 80 per 100,000 males and at 47 per 100,000 females in 2001. For Québec, they are 108 per 100,000 males and 51 per 100,000 females, which translates into 6,500 new cases of lung cancer and 5,600 deaths due it (NCIC, Canadian Cancer Statistics, 2001].

The presence of a radiographically detected pulmonary lesion (nodule or mass) is reason to suspect lung cancer. To determine how a patient with lung cancer should be managed and what his or her prognosis is, it is essential to differentiate, histopathologically, between small-cell lung cancer and non-small-cell lung cancer (NSCLC) [Lacasse, 2000].

Small-cell lung cancer (SCLC) accounts for about 20% of all primary lung cancers. Patients with this type of cancer have a very poor prognosis, with 5-year survival rates of less than 1%. Non-small-cell lung cancer (NSCLC) is often limited to the chest upon initial staging, and 5-year survival rates for these patients are 60 to 70% for stage I[*], 30 to 50% for stage II, 5 to 30% for stage III and less than 2% for stage

---

[*] Staging in accordance with 1997 UICC recommendations.

IV cancers [Klemenz and Taaleb, 2000].

Despite the intention to treat NSCLC with curative-intent surgery, the lesions are not resectable in 5 to 7% of operated patients, and 14% of patients die during the first year following curative-intent surgery. These results underscore the major need to improve the strategy for diagnosing lung cancer [Klemenz and Taaleb, 2000].

The conventional methods used to characterize the pulmonary nodule (bronchoscopy, transthoracic needle biopsy) and to determine the extent of the disease when a diagnosis of cancer is made (axial CT scan of the chest, bone scan, abdominal ultrasound and mediastinoscopy) are imperfect and often invasive. Furthermore, it is common for these conventional methods to underestimate the extent of the disease, which results in inadequate patient management [Lacasse, 2000].

4.1.1.2 The role of PET

In NSCLC, the following uses were examined: characterizing the solitary pulmonary nodule (SPN), initial staging (detecting distant and mediastinal metastases), monitoring response to therapy and detecting recurrence or residual tumors following therapy.

On the whole, PET appears to perform better than the conventional invasive investigative methods (e.g., CT-guided transthoracic biopsy). Furthermore, it does not involve any complications.

4.1.1.3 Previous positions and updates

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed additional light on the subject, if need be. The complete list of positions is presented in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Characterizing the solitary pulmonary nodule (SPN)**

✿	Use recognized by the HCFA, MSAC and BCBSA and the assessment agencies MHTAC, AHTAA and INAHTA. The VA-TAP recognizes PET's potential for this use (✿).

Following the HCFA's 1998 decision, Medicare covers PET scans in patients with an undetermined solitary pulmonary nodule (SPN) (as a substitute for transthoracic biopsies and surgical excisions) [Tunis et al., 2000].

The MSAC cites three studies concerning the diagnosis of solitary pulmonary lesions [Lowe et al., 1998; Prauer et al., 1998; Dewan et al., 1997]. Lowe et al. obtained a sensitivity of 92% and a specificity of 90% for PET in such cases, results which were supported by those of Prauer et al. (sensitivity of 90% and specificity of 83%). The MSAC concluded that "[t]he potential value for PET in this indication is in the avoidance of biopsy in negative lesions. However, since FNAB is still a reasonably low-risk procedure, PET would mainly be of value for lesions considered to be unsuitable for FNAB [because of severe lung disease or because the lesion is in an unfavourable location] or for those with a very low post-test probability of malignancy" [Ghersi et al., 2000].

Up to February 2001, no new studies on the characterization of the SPN were identified. Given that there is no noninvasive examination for differentiating between a benign nodule and a malignant one at this time, that the prevalence of malignant nodules is high in Québec and that most pulmonary nodules are malignant (personal communication from the advisory committee, 2001), PET would be useful in such cases. The MSAC's and HCFA's conclusions are repeated here: The characterization of the SPN by PET is considered a recognized use.

- **Staging: distant and mediastinal metastases**

✿	Use recognized by the HCFA, BCBSA-TEC, MSAC, MHTAC and INAHTA. According to the VA-TAP, PET has potential for detecting mediastinal metastases.

Following the HCFA's 1998 decision, Medicare covers PET scans for the initial staging of lung cancer in patients diagnosed with NSCLC [Tunis et al., 2000].

The MSAC report reviews 14 relevant studies published before the end of 1999. It states that PET is more accurate than conventional imaging in detecting distant and mediastinal metastases and that the evidence is significant with regard to a change in management before surgery or radiation therapy, although there is no evidence at this time to quantify the impact of these changes on health outcomes. It concludes that "[d]espite the methodological limitations of some of these studies, it is reasonable to conclude that PET significantly improves the diagnostic accuracy of staging the mediastinum over conventional imaging, particularly when PET is considered in addition to CT" [Ghersi et al., 2000].

Our searches (Appendix 8) identified six new studies on PET for staging NSCLC. Data on the sensitivity and specificity of PET are presented in five of them, although only four compared it with computed tomography. The four studies in question are those by Gupta et al. [2000] (25 patients), Vanuytsel et al. [2000] (105 patients), Pieterman et al. [2000] (102 patients) and Hara et al. [2000] (29 patients) (see Appendix 9 for the methodological quality of these studies). In these four studies, the sensitivity of PET was superior to and its specificity greater than or equal to those of computed tomography. In Vanuytsel's study, better sensitivity and equal specificity were achieved with PET + CT than CT alone. Only one study, that by Gupta et al., reports that the sensitivity of PET depends on the size of the lesions, stating that it is less (82%) for nodules of < 1 cm.

The improvement achieved with PET in these four studies was similar to that reported in the studies evaluated by the Australian authors: sensitivity is improved by 10% or more, while the improvement in specificity is between 0 and 25%.

A meta-analysis performed by Dwamena [1999] compares PET for the mediastinal staging of non-small-cell lung cancer in 14 studies and computed tomography in 29 but does not provide a matched comparison between the simultaneous, comparative studies. In addition, five of the 14 studies of PET had already been reviewed in the Australian report. This meta-analysis concludes that PET is superior to computed tomography.

Another recently published meta-analysis [Gould et al., 2001] does not compare PET to any other imaging method for diagnosing pulmonary nodules and lesions. However, the authors conclude that FDG-PET is a noninvasive test with acceptable efficacy, although there are few data for nodules of < 1 cm. They state that, in clinical practice, FDG-PET has high sensitivity but intermediate specificity in determining malignancy of a lesion.

With surgical intervention avoided in some patients, PET could also be cost-effective [Gambhir et al.,1998]. Section 4.4 examines this in greater detail and provides a decision model for NSCLC.

This update shows that the clinical utility of PET in staging NSCLC is supported by new data demonstrating superior sensitivity and equal or superior specificity, which facilitates patient management in the immediate term.

- **Monitoring response to therapy**

✿	The MSAC and VA-TAP recognize that PET has potential for this use. The HCFA does not cover PET scans for monitoring response to therapy.

In its report, the MSAC mentions the potential role of PET in monitoring response to therapy (chemotherapy or radiation therapy), but this use was not thoroughly examined in its March 2000 assessment. It does, however, mention two studies [Kiffer et al., 1998; Nestle et al., 1999] that report a change in the radiation field in close to one third of cases after a PET scan. However, Kiffer et al.'s study was a retrospective analysis, and that of Nestle et al. involved a series of selected cases, with the result that the real impact of PET on the change in management cannot be assessed. The MSAC believes that "[f]or patients whose disease is potentially curable but who present a poor surgical risk, radical radiotherapy may be given. In such cases, the role and value of PET in the initial staging and in determining whether aggressive or palliative radiotherapy is given should be similar to its role in preoperative surgical imaging."

No new studies on monitoring response to therapy were identified. The MSAC's conclusion is repeated here: PET could play a role in therapeutic response monitoring in NSCLC, although hard data are needed in order to conclude that it is clinically effective.

- **Detecting residual or recurrent tumors**

✿/✿	The HCFA recommends that this use be covered, and the MHTAC (Minnesota) recognizes this use. The MSAC and VA-TAP recognize PET's potential for this application.

In its 2000 decision, the HCFA made a recommendation to Medicare that it extend its coverage of PET to the detection of residual or recurrent NSCLC tumors, the main rationale being the study by Bury et al. [1999], which involved 126 patients. Although the PET results were not analyzed in a blinded fashion, the HCFA calls attention to the study's rigorous design and the large patient sample. The comparisons showed that PET was superior to computed tomography in detecting residual or recurrent tumors, with a sensitivity of 100% (compared to 72% for computed tomography) and equivalent specificity (90%) [Tunis et al., 2000].

No new studies on the detection of recurrent or residual NSCLC tumors were identified. Although the HCFA recommends coverage of PET for detecting recurrent or residual tumors, this recommendation is based on just one study. This use of PET is therefore a potential application, according to the MSAC's conclusions.

4.1.1.4 Conclusions

In non-small-cell lung cancer, the clinical utility of PET is

recognized for the following uses:

- characterizing the solitary pulmonary nodule;
- initial staging when a diagnosis of non--small-cell lung cancer is made, including:
  - the detection of mediastinal lymph node metastases; and
  - the detection of distant metastases;

and has potential for:

- monitoring response to therapy; and
- detecting recurrent or residual tumors.

4.1.2 Colorectal cancer

4.1.2.1 General data

It is estimated that there will be 17,200 new cases of colorectal cancer and 6,400 deaths due to colorectal cancer in Canada in 2001. In Québec, for the same year, the number of new cases of colon and rectal cancer is estimated at 4,300 and the number of deaths at 2,100 [NCIC, Canadian Cancer Statistics, 2001].

The examination of choice for initially diagnosing colon cancer and biopsying suspicious lesions (polyps) is the colonoscopy [Laplante, 2000]. Barium enemas, a complete blood count, a carcinoembryonic antigen (CEA) assay and other tests (electrolytes, enzymes, etc.) also aid in the diagnosis. Treatment is essentially surgical in nature and consists in excising the tumors. This will be the only intervention in cases that are diagnosed early. In more advanced cases, radiation therapy and chemotherapy may be added.

The frequent sites of metastasis during recurrence are the pelvic region, liver and lungs. Recurrences occur in 75% of patients, and their diagnosis is somewhat problematic, especially in the case of recurrences in the region of the anastomosis, local recurrence, lymph node metastases and distant metastases. The therapeutic outcomes in these patients mainly depend on the recurrence being diagnosed early. The usual follow-up consists of a postoperative examination with tumor markers, mainly CEA [Dimitrakopoulou-Strauss, 2000; Laplante, 2000].

In the presence of an elevated CEA, the best methods for diagnosing recurrent colorectal cancer include the double-contrast barium enema, rectosigmoidoscopy, endoscopic ultrasound (EUS), computed tomography and magnetic resonance imaging. The efficacy of EUS is superior to that of computed tomography and magnetic resonance imaging. The latter two techniques are useful for detecting an increase in lymph node size and detecting distant metastases, although their efficacy in detecting a local recurrence is not entirely satisfactory [Dimitrakopoulou-Strauss, 2000].

Another method for detecting local recurrence is the CT-guided biopsy, an invasive procedure that cannot be used as a diagnostic standard because, although a positive result is clearly indicative of tumor recurrence, a negative result cannot rule out the presence of a tumor. Immunoscintigraphy is another method that can be used to detect recurrence, but its sensitivity depends on several factors, including the physical properties of the radionuclide, the labelling technique, the location and size of the lesions, and the protocol used during the examination [Dimitrakopoulou-Strauss, 2000].

4.1.2.2 The role of PET

In colorectal cancer, the following uses were examined: diagnosing the primary lesion; monitoring response to therapy; evaluating regional lymph nodes; detecting hepatic and extrahepatic metastases in cases of suspected local recurrence; detecting recurrence; differentiating between recurrence and postoperative scar; and determining the location of recurrent tumors in the context of a rising CEA level.

It is for detecting metastases that PET appears to be most beneficial in colon cancer, as it enables one to plan the simultaneous resection of the metastases or to avoid a major operation in the presence of generalized disease. For detecting hepatic or extrahepatic metastases and differentiating postoperative scar from local recurrence, PET seems to be more sensitive then computed tomography. However, it should be noted that PET can yield false-positive results during the six months following radiation therapy because of the inflammatory reaction

[CMI: Beanlands et al., 1999; Laplante, 2000; Létourneau, 2000].

4.1.2.3 Previous positions and updates

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Diagnosing the primary lesion**

✿/✿	Only the MHTAC mentions PET in connection with diagnosing colorectal cancer. However, the members of the FMSQ's committee consider that there is no evidence to support this use.

No new studies on diagnosing the primary lesion in colorectal cancer by FDG-PET were identified up to February 2001.

- **Monitoring response to therapy**

✿	Only the MHTAC and the AHTAA mention PET's potential for this use.

No new studies on monitoring response to therapy with FDG-PET were identified up to February 2001.

- **Detecting hepatic and extrahepatic metastases in cases of suspected local recurrence**

✿/✿	The HCFA, BCBSA-TEC and MSAC support this use. The MHTAC and VATAP recognize PET'S potential for this application

The conclusions of the Australian report and those in the HCFA's coverage decision are based on two high-quality studies with a sufficiently large number of patients [Flamen et al., 1999 (103 patients) and Valk et al., 1999 (155 patients)]. In addition, similar results had been obtained in two smaller studies previously published by Ogunbiyi et al. [1997, 47 patients] and Delbeke et al. [1997, 45 patients]. Valk et al. obtained a sensitivity of 95% with PET for the detection of hepatic metastases versus 84% with computed tomography (specificity: 100% for PET vs. 95% for computed tomography) and a sensitivity of 90% with PET versus 58% with computed tomography for extrahepatic metastases. Flamen et al. obtained similar results. The sensitivity of PET was 4% higher than that of computed tomography for hepatic metastases and 38% higher for extrahepatic metastases (specificity of PET greater than or equal to that of CT).

The studies by Flamen et al. and Valk et al. show that PET is superior to computed tomography in detecting hepatic and extrahepatic metastases in cases of suspected local recurrence [Ghersi et al., 2000; Tunis et al., 2000].

For detecting hepatic metastases in cases of local recurrence of colorectal cancer, the MSAC concludes that "the concordance between CT and PET results is high, though PET offers the advantage of detecting a small number of cancers that would have been missed by CT.... Little is known about how outcomes are affected by changing management in people who have abnormalities that are detectable only on PET. Although there is evidence that chemotherapy for early asymptomatic disease prolongs survival..., it is unclear if this advantage extends to disease detectable only on PET and whether there are improvements in quality of life" [Ghersi et al. 2000].

For the detection of extrahepatic metastases, the MSAC concludes that "the relatively large improvement in sensitivity of PET in the detection of extrahepatic metastases has a major potential impact on avoiding surgery and its human and financial costs. The effect of avoiding surgery on survival and quality of life has not been directly assessed" [Ghersi et al. 2000].

Three new studies of suitable quality (see Appendix 9) were identified up to February 2001 [Imdahl et al., 2000, 71 patients; Zhuang et al., 2000, 80 patients; and Staib et al., 2000, 100 patients].

For the detection of metastases, Imdahl et al. report a sensitivity of 100% for PET (vs. 87% for computed tomography and 100% for MRI, although MRI was performed in only 22 patients) and a specificity of 98% (vs. 91% for computed tomography and 100% for MRI). Furthermore, the treatment could have been modified in 16/71 patients, thanks to PET. The results of the study by Zhuang et al. are equally robust, with PET having detected extrahepatic lesions in 6/80 patients versus computed tomography, which did not detect any. Staib et al.'s results confirm these figures, with a sensitivity of 100% for PET compared to 97% for conventional imaging (specificity: 99% for PET vs. 96% for computed tomography). Accordingly, surgery in these patients can therefore be avoided with PET.

A new study, by Strasberg et al. [2001], involved 43 patients with hepatic metastases identified by computed tomography who were considered suitable candidates for surgery. PET identified extrahepatic metastases in 10 of these patients, thus avoiding unnecessary surgery.

This update lends, by way of new data, support to the MSAC's and HCFA's conclusions. The most important clinical contribution of PET in this type of cancer consists in identifying patients with extrahepatic metastases, in whom surgery is contraindicated, which would reduce the morbidity and hospital costs associated with such surgery.

The clinical utility of PET in detecting metastases from recurrent colorectal cancer is recognized.

■ **Recurrence: Detection, differentiation of postoperative scar and determination of the location of recurrent tumors in the context of a rising CEA level**

✿	The HCFA recognizes the use of PET for detecting recurrent tumors (in conjunction with computed tomography), but the MSAC, MHTAC, AHTAA, VATAP and INAHTA only recognize its potential in this regard.
✿	Debate: The HCFA and MSAC recognize the use of PET for differentiating recurrence from postoperative scar, while the BCBSA-TEC states that there is no evidence in this regard. The AHTAA recognizes PET's potential for this application.
✿	Up until 2000, the HCFA covered PET scans only for determining the location of recurrent colorectal tumors when indicated by rising CEA levels (restriction lifted in 2000). The BCBSA-TEC and AHTAA recognize this use.

In its March 2000 report, the MSAC recommends that PET be covered on an interim basis for the evaluation of residual abnormalities on conventional imaging in patients who are symptomatic following definitive treatment for colorectal cancer. This decision was based on the two studies mentioned earlier (Flamen et al., 1999; Valk et al., 1999], which show that PET is superior to computed tomography in detecting recurrent colorectal cancer [Ghersi et al., 2000].

Following the HCFA's decision, Medicare has, since 1998, been covering PET scans for determining the location of recurrent tumors in the context of a rising CEA level. In its 2000 decision, the HCFA lifted the restriction of an elevated CEA. This use is now covered in the context of abnormal clinical findings during posttreatment follow-up. In addition, the HCFA extended its PET coverage recommendation for colorectal cancer to include differentiating between local recurrence and postoperative scar. Although the six studies reviewed by the organization were characterized by certain methodological biases, the HCFA maintains that PET scanning could have the ability to influence posttest probabilities such that patients and their physicians can choose an appropriate biopsy strategy, which would increase the chances for curative resection [Tunis et al., 2000].

No new studies on the utility of PET in differentiating between recurrence and postoperative scar or in evaluating residual lesions after definitive treatment were identified.

As for determining the location of recurrent tumors in the context of abnormal clinical findings after curative-intent treatment, Imdahl et al. [2000] report that, in their study, PET provided additional information in 86% of the cases compared to conventional imaging, which had an impact on the surgical decision in 61% of the cases. Similarly, the results of the study by Staib et al. [2000] show a sensitivity of 98% for PET (vs. 91% for computed tomography and 76% for the CEA assay) and a specificity of 90% (vs. 72% and 90% for computed tomography and the CEA assay, respectively).

This update shows that PET seems to improve the detection of recurrence (in the context of abnormal clinical findings). No new studies on differentiating between residual tumor and postoperative scar (or radionecrosis) were identified. The MSAC's and HCFA's conclusions are repeated here: The clinical utility of PET in detecting recurrence, differentiating between recurrence and postoperative scar, and determining the location of recurrent tumors in the context of abnormal clinical findings is recognized.

4.1.2.4 Conclusions

In colorectal cancer, the clinical utility of PET

is recognized for the following uses:

- detecting preoperatively hepatic and extrahepatic metastases in patients in whom a localized recurrence is detected;
- determining the location of recurrent tumors in the presence of clinical symptoms or abnormal paraclinical findings (conventional imaging, CEA, etc.); and
- differentiating between recurrence and postoperative scar in the context of diagnostic imaging that shows abnormalities;

has potential for:

- monitoring response to therapy;

and is not recognized for:

- diagnosing the primary lesion.

4.1.3 Melanoma

4.1.3.1 General data

The incidence of melanoma has increased steadily over the past few years. Thelen and Bares [2000] cite a melanoma incidence rate for whites in Europe of 8 per 100,000, with the rate increasing up to 20 per 100,000 near the equator.

It is estimated that there will be 3,800 new cases of melanoma and 820 melanoma deaths in Canada in 2001, with 570 new cases and 140 deaths in Quebec [NCIC, Canadian Cancer Statistics, 2001].

One of the characteristics of melanoma is its rapid metastasis. For staging regional lymph nodes, high-resolution ultrasound is the most widely used method. Chest x-rays and abdominal ultrasound are used as well. When the results are inconclusive or reveal an abnormality, CT scans of the chest, abdomen and, if applicable, the head are performed [Thelen and Bares, 2000].

There is currently no curative treatment for melanoma with widespread metastases.

4.1.3.2 The role of PET

In melanoma, the following uses were examined: diagnosis, initial staging, evaluating lymph nodes, detecting extranodal metastases in the context of a preoperative workup or of a posttreatment or postoperative follow-up, and evaluating recurrence during a postoperative follow-up.

PET is less effective than conventional diagnostic methods for detecting the primary lesion and diagnosing local recurrence and therefore cannot, at this time, be used as a diagnostic standard, according to Thelen and Bares [2000]. It can however, be used to visualize suspected malignant lesions in structures that appear normal on clinical examination (e.g., normal-size lymph nodes), thus permitting early localization of a tumor and thus improving the patient's prognosis. Furthermore, the detection of widespread metastases can spare the patient "extensive, mutilating surgery" [Eigtved et al., 2000].

4.1.3.3 Previous positions and updates

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Diagnosing the primary lesion**

✿	The only organization that mentions this use of PET is the INAHTA, which recognizes its potential in this regard.

Up to February 2001, no new studies on the diagnosis of the primary melanoma tumor were identified.

- **Initial staging**

✿/✿	The HCFA, MSAC and BCBSA recommend coverage of PET for the staging of melanoma. The INAHTA recognizes its potential in this regard.

The Australian report identified 11 studies on the detection of melanoma metastases that qualified according to the selection criteria. Only four of these studies were actually comparative (one additional study compared the sensitivity rates but not the specificity rates - See Appendix 9). In the first of these studies [Blessing et al., 1995, 20 patients], computed tomography was not found to be more accurate than ultrasound. In the second study [Valk et al., 1996, 35 patients], the sensitivity of PET and that of computed tomography were comparable (96% and 94%), but PET's specificity was superior, being 55% versus 12%, which is low. In the third study [Holder et al., 1998, 76 patients), the higher sensitivity of PET (94%) versus that of computed tomography (83%) was achieved at the cost of low specificity (55% for PET and < 84% for computed tomography). The fourth study, the most robust and rigorous one [Rinne et al., 1998] involved 52 patients. The sensitivity of PET was 100%, that of conventional imaging 85%. This sensitivity was achieved while at the same time maintaining 96% specificity compared to 68% for conventional imaging.

Based on these studies, mainly that of Rinne et al. [1998], the Australian report concludes that "PET appears to have improved diagnostic accuracy over conventional imaging in the detection of metastatic lesions, but methodological limitations of the studies should be borne in mind."

Ten studies published between 1999 and February 2001 were identified. Only three of them were comparative, and they were of low methodological quality. The first one [Paquet et al., 2000], which involved 24 patients, reported equivalent accuracy for PET and computed tomography (> 80%), which is not surprising, given the small, statistically insufficient patient sample (study rated D).

The second study, rated C, involved 38 patients [Eigtved et al., 2000] and reports 97% sensitivity for PET and 62% for conventional imaging, with 62% specificity (vs. 22% for conventional imaging). The third study, rated D, involved 68 patients with advanced melanoma [Dietlein et al., 1999]. It merely concludes that "PET detected fewer pulmonary and hepatic metastases..., but more lymph node and bone metastases than conventional radiology or CT."

Since the new studies are of inadequate methodological quality, they add nothing to the MSAC's and HCFA's conclusions, which are that the clinical utility of PET for initial staging of melanoma is recognized.

■ Evaluating lymph nodes

✿	The HCFA, MSAC and BCBSA-TEC consider that there is no evidence to support the use of PET for this application because of its low sensitivity for micrometastases. The AHTAA acknowledges that the evidence is lacking, but that there is nonetheless potential for this application.

Based on the results of a study by Wagner et al. [1999], the MSAC concludes that PET is not accurate for diagnosing micrometastases. Wagner et al. reported quite low results for the diagnosis of lymph node metastases compared to lymph node biopsy. They state that if PET is used to screen patients for the purpose of resecting seemingly isolated metastases, micrometastatic disease in other sites cannot be ruled out. The MSAC states that "[t]his does not negate PET's potential role in identifying patients for whom surgery would achieve local control and delay the onset of major symptoms or complications from metastatic disease. However, the value of PET in changing management to avoid surgery in those patients with early metastatic disease is unclear and would require long-term controlled cohort studies...before any conclusions could be drawn." [Ghersi et al., 2000].

The HCFA concludes that, since there is a lack of evidence to the contrary, certain strongly negative studies (e.g., that of Wagner et al., 1999, mentioned above) form the basis for its refusal to cover PET for lymph node evaluation [Tunis et al., 2000].

A recently published meta-analysis [Mijnhout, 2001] of 11 studies, several of which were mentioned above (initial staging), draws the following conclusion: PET seems to be highly accurate in detecting metastases, but it seems to be less accurate for regional than systemic staging and for stages I and II disease than stage III melanoma.

Two fairly recent studies [Tyler et al., 2000; Wagner et al., 1999] (that of Wagner et al. was used by the MSAC and HCFA to draw their conclusions), illustrate, in part, the large disparity between the performance results reported in various studies. Although Tyler et al.

examined PET in stage III melanoma (in lymph node metastases), their sensitivity of 87% was obtained with a specificity of only 44%. Wagner et al.'s study [1999], which is of high-quality, found that PET's sensitivity for occult lymph node metastases was only 17%, with 96% specificity. Sentinel lymph node biopsy, on the other hand, had a sensitivity of 95%, with 100% specificity.

It seems to be accepted that PET is more sensitive in detecting disease with metastatic dissemination but that it is insensitive in detecting micrometastases from early-stage lesions. In short, the evidence concerning the improvement in diagnostic accuracy for lymph node metastases with PET is very limited. Wagner et al.'s study shows that PET cannot replace sentinel lymph node biopsy for detecting regional lymph node metastases during initial staging or during posttreatment monitoring.

Since no new studies that could support or contradict the MSAC's or HCFA's conclusions were identified in the update, the clinical utility of PET in evaluating regional lymph nodes is not recognized.

- **Extranodal metastases (preoperative staging or postoperative follow-up)**

✿	The HCFA, MSAC and BCBSA-TEC recommend coverage of PET for the detection of extranodal metastases during initial staging or in the context of a postoperative follow-up. The AHTAA mentions PET's potential for detecting metastases in cases of advanced lesions (Clark III and IV).

In its conclusions, the MSAC states that, in the studies where metastatic disease was not detected by conventional imaging modalities, PET was reported to have nearly 100% sensitivity [Steinert et al., 1995; Rinne et al., 1998; and Holder et al., 1998]. However, the authors also mention the possibility of selection bias in some of these studies, since only PET-positive lesions were confirmed histologically. Furthermore, they once again cite Wagner et al.'s study [1999], which reports a very low sensitivity for PET and in which histological confirmation was done in entire series of cases. Nevertheless, the MSAC recommends coverage of PET on an interim basis for the preoperative evaluation of patients being considered for surgical resection of apparently limited metastatic disease from melanoma [Ghersi et al., 2000].

For its part, the HCFA bases its recommendation that PET be covered for the detection of extranodal metastases in the context of a postoperative follow-up on two studies cited by the MSAC [Rinne et al., 1998; Holder et al., 1998] and on that of Valk et al. [1996]. Rinne et al.'s study [1998] provides promising data to support the use of PET when added to conventional imaging in this situation, despite the lack of evidence of health benefits. The HCFA draws the following conclusion: "However, it is likely that the expected clinical impact will be limited. In patients where there is a concordant result..., there will be no significant change in management. The true impact will likely be realized when PET detects lesions missed by conventional imaging since patients will receive necessary treatment in a timely fashion without the delay from underdiagnosis" [Tunis et al., 2000].

None of the ten new studies identified up to February 2001 is of sufficient quality to confirm or invalidate the MSAC's or HCFA's conclusion, which is as follows: The clinical utility of PET in evaluating extranodal metastases is recognized.

- **Preoperative evaluation of recurrence/postoperative follow-up**

✿	The HCFA recommends coverage of

	PET for the evaluation of recurrence when used as an alternative to a gallium scan. The AHTAA also recognizes this use. The MSAC makes no mention of it.

Since there are no new studies contradicting its 1999 conclusion, the HCFA renewed, in December 2000, its decision concerning PET coverage for the evaluation of melanoma prior to surgery when used as an alternative to a gallium scan.

No new studies on the clinical utility of PET in the evaluation of recurrent melanoma were identified up to February 2001.

4.1.3.4 Conclusions

In melanoma, the clinical utility of PET

is recognized for the following uses:

- detecting extranodal metastases during initial staging or in the context of a postoperative follow-up;
- evaluating a potentially treatable recurrence; and

is not recognized for:

- diagnosing the primary lesion; or
- detecting lymph node metastases.

4.1.4 Head and neck cancer

4.1.4.1 General data

Head and neck tumors account for about 3 to 5% of all malignant tumors and occur mainly in males (male-to-female ratio = 6:1). In general, the worldwide incidence is about 20 in 100,000 (males), and the mortality rate, in 1994, was 6.3 in 100,000 males and 1.1 in 100,000 females [Bender and Straehler-Pohl, 2000].

It is estimated that there will be 3,100 new cases of mouth cancer and 1,250 new cases of cancer of the larynx in Canada in 2001, with 1,570 resulting deaths. In Québec, in 2001, it is estimated that there will be 1,290 and 560 new cases of mouth and laryngeal cancer, respectively, with about 450 resulting deaths [NCIC, Canadian Cancer Statistics, 2001].

The diagnosis of head and neck tumors is based mainly on a physical examination, together with ultrasound, computed tomography, magnetic resonance imaging and biopsy. In general, palpation and visual examination seem to have better specificity than morphological imaging, as they provide information on tumor structure and consistency. The use of imaging techniques permits a better evaluation of the size, structure, relationship to the adjacent issues and extent of the disease. There are limitations when the lesions are small and without any morphologic change (micrometastases, or small metastases in normal-size lymph nodes, etc.); when lymph nodes have increased in size in the absence of any typical signs of malignancy; and when the anatomical regions have been deformed by surgery or radiation therapy, thus complicating the task of differentiating between postoperative scar and tumor [Bender and Straehler-Pohl, 2000].

Newly diagnosed malignant lesions are considered "unknown primaries" in 2% of cases. These tumors often manifest as adenopathies in lymph nodes throughout the body (37%), and 31% of them occur in the head and neck region [Jungehulsing et al., 2000; Scheidhauer et al., 2000]. Squamous-cell cervical metastases from unknown primary sites probably originate from an unknown head and neck primary, since the tendency with head and neck tumors is that they are originally regional, not distant, metastases, which makes them potentially curable [Lassen et al., 1999; Dr. Jacques Laplante, personal communication, 2001].

4.1.4.2 The role of PET

In head and neck cancer, the following uses were examined: identifying an unknown primary tumor, staging regional lymph nodes, monitoring response to therapy, detecting recurrence or residual tumor, and differentiating postoperative scar.

It has been suggested that the use of functional imaging techniques improves tissue evaluation and probably provides clues as to a tumor's histology. This is very important because typical functional changes can occur at an early stage, often well before morphological changes can be detected [Bender and Straehler-Pohl, 2000].

4.1.4.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Identifying an unknown primary tumor in the presence of cervical lymph node metastases**

✿ ✿	The HCFA and BCBSA-TEC recommend coverage for PET for this use when conventional imaging is unable to identify the primary tumor. The AHTAA considers that the data are insufficient to support this use, while the VA-TAP recognizes PET's potential for this application.

The MSAC does not mention unknown primary tumors in its March 2000 report. It states that there are several other potentially important uses of PET but that they were not studied in its report and stresses that it should not be assumed that PET has no role to play in the uses that are not mentioned in its assessment.

Of the eight studies identified on the subject, the HCFA selected four for review, based on their ability to demonstrate the incremental benefit of this use of PET. The four studies showed a pooled true-positive rate of 30% in patients who had negative findings on examination and conventional imaging [Tunis et al., 2000].

PET seems to have positive utility in identifying an unknown primary tumor when there are cervical node metastases. When the primary tumor is identified by PET and when this is confirmed by biopsy, directed tumor management is initiated, thus avoiding the morbidity associated with unnecessary radiation therapy or surgery. Long-term survival has thus far not been studied. Although management is improved, it is not certain that this leads to better health outcomes.

The HCFA concludes that it is reasonable to support coverage of PET for identifying unknown primary tumors, since this could be beneficial in nearly one third of patients in whom diagnosis might otherwise have failed [Tunis et al., 2000].

Our literature searches identified four new studies [Jungehulsing et al., 2000; Bohuslavizki et al., 2000; Perie et al., 2000; and Lassen et al., 1999] on the identification of unknown primary tumors, although none of these studies is of sufficient quality (see Appendix 9). The HCFA's conclusion is therefore repeated here: The clinical utility of PET in identifying unknown primary tumors is recognized.

- **Staging cervical lymph node metastases**

✿	The HCFA and BCBSA recommend

✿	coverage of PET for the initial staging of cervical lymph nodes involved in metastatic disease. In the AHTAA's opinion, there is no evidence to support this use. The VA-TAP recognizes PET's potential for staging cervical lymph node metastases.

Based on the BCBSA-TEC's conclusions and on a small, methodologically robust study (n = 19) [Wong et al., 1996] that is supported by data from other, less rigorous studies, the HCFA concludes that PET should be covered for staging cervical lymph nodes when there is metastatic disease. The results of Wong et al.'s study showed that computed tomography alone correctly staged the disease in 69% of the patients, while computed tomography followed by PET correctly staged it in 92% of the patients [Tunis et al., 2000].

No new studies on staging head and neck cancer were identified. The HCFA's conclusion is stated here: The clinical utility of PET is recognized for staging cervical lymph nodes.

- **Monitoring response to therapy**

✿	In the AHTAA's opinion, there is no evidence to support this use, while the VA-TAP recognizes PET's potential for such use, although it states that further studies are required. The HCFA does not cover PET for monitoring response to therapy.

No new studies were identified up to February 2001. PET has potential clinical utility in this application.

- **Detecting recurrence or a residual tumor and differentiating postoperative scar**

✿/✿	The HCFA recommends coverage of PET for this use. The MHTAC and VA-TAP recognize PET's potential for this application. The AHTAA recognizes its potential in cases where there are negative findings on computed tomography or magnetic resonance imaging.

The HCFA reviewed 11 comparative studies in order to make its coverage decision regarding PET for detecting recurrence and residual tumors and for differentiating them from postoperative scar. Six of the studies showed PET to have superior sensitivity and specificity than computed tomography, magnetic resonance imaging and the physical examination [Lowe et al., 2000; Wong et al., 1997; Anzai et al., 1996; Farber et al., 1999; Rege et al., 1994; and Kao et al., 1998]. Four of them reported neutral or mixed rates [Hanasono et al., 1999; Manolidis et al., 1998; Nowak et al., 1999; and Greven et al., 1997], and the last one [Paulus et al., 1998] reported a less favourable diagnostic performance with PET in relation to computed tomography. The HCFA bases itself on the study by Wong et al. [1996] to support its coverage decision, despite the small sample size in this study (which was of relatively strong design), stating that a more informed clinical decision probably leads to improved health outcomes [Tunis et al., 2000].

Four new studies were identified up to February 2001 [Di Martino et al., 2000; Lowe et al., 2000; Lonneux, 2000; and Farber et al., 1999]. They seem to suggest that PET is superior to conventional imaging (computed tomography, MRI, ultrasound), but these studies were of low methodological quality (grades C or D; see Appendix 9).

Since this update did not identify any studies supporting or contradicting the HCFA's conclusion concerning head and neck cancer, that conclusion is stated here: The clinical utility of PET in detecting recurrent disease and residual tumors in the presence of abnormalities on conventional imaging is recognized.

4.1.4.4 Conclusions

In head and neck cancer, the clinical utility of PET

is recognized for:

- identifying an unknown primary tumor in the presence of cervical node metastases;
- staging cervical lymph nodes when there are negative findings on conventional imaging; and
- detecting recurrent disease or residual tumor and differentiating postoperative scar;

and is not recognized for:

- monitoring response to therapy.

4.1.5 Lymphoma

4.1.5.1 General data

It is estimated that there will be 6,200 new cases of non-Hodgkin's lymphoma and 2,700 deaths due to this type of cancer in Canada in 2001. In addition, it is estimated that there will be 810 new cases of Hodgkin's lymphoma and 120 deaths due to this disease. In Québec, the estimates are 1,590 new cases of non-Hodgkin's lymphoma and 580 deaths [NCIC, Canadian Cancer Statistics, 2001].

The introduction of computed tomography and magnetic resonance imaging led to vast changes in the diagnostic imaging of lymphomas. Although there have been some methodological improvements, these changes have apparently now slowed down. Because of the limitations of diagnostic methods like ultrasound, staging malignant lymphoma presently depends on an increasing number of diagnostic methods specific to the disease of interest (organ system-specific). These tests are associated with significant costs in terms of time and logistics, to say nothing of the considerable patient discomfort associated with the usual procedures for staging lymphoma (bone marrow aspiration and biopsy, CT scans of the abdomen, pelvis and chest, gallium imaging and, in some cases, bone imaging) [CMI: Beanlands et al., 1999; Moog, 2000].

4.1.5.2 The role of PET

In lymphoma, the following uses were examined: initial staging, posttreatment follow-up and monitoring response to therapy.

The numerous modalities used for the usual staging of lymphoma can be replaced by a single PET scan. Furthermore, PET often reveals a more advanced stage of the disease and leads to more aggressive management. It has been suggested that PET is as useful for evaluating response to therapy as it is for staging. An American study [Young et al., 1997] found that upon using PET prior to treatment and again after two cycles of chemotherapy for evaluating the intermediate response to treatment, the mortality rate due to lymphoma was reduced by one half in relation to the national average rate [CMI: Beanlands et al., 1999].

For example, PET is a one-day procedure that is more advantageous than gallium imaging because it has higher resolution, permits better dosimetry, induces less intestinal activity and shows quantitative potential. Furthermore, FDG-PET can be used to evaluate residual lesions posttreatment with a high level of accuracy [Laplante, 2000].

4.1.5.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

■ Initial staging and posttreatment follow-up

✿/✿	The HCFA and BCBSA-TEC both recommend coverage of PET for these uses. The MHTAC and AHTAA recognize PET's potential for these applications.

The MSAC does not mention Hodgkin's or non-Hodgkin's lymphoma in its March 2000 report. It states that there are several potentially important uses of PET that were not examined in its report and stresses that it should not be assumed that PET has no role to play in the uses that are not mentioned in its assessment.

Since 1999, the HCFA has recommended coverage of PET for initial and posttreatment staging when used as a substitute for a gallium scan.

The BCBSA-TEC identified 14 studies published between April 1997 and March 2000 on the staging of Hodgkin's and non-Hodgkin's lymphoma during initial staging or posttreatment follow-up [Bangerter et al., 1999; Jerusalem et al., 1999; Moog et al., 1999; Zinzani et al., 1999; Stumpe et al., 1998; Hoh et al., 1997; Bares et al., 1993; Carr et al., 1998; de Wit et al., 1997; Rodriguez et al., 1997; Bangerter et al., 1998, Rodriguez et al., 1995; Leskinen-Kallio et al., 1991; and Okada et al., 1994]. Of these studies, three compared PET with conventional imaging, and two included data concerning sites with and without disease for PET and computed tomography. These two studies showed that PET provides greater diagnostic accuracy than computed tomography. The BCBSA-TEC concludes that when PET is added to conventional imaging, it provides useful information for selecting effective treatment appropriate to the correct stage of disease.

The update to February 2001 identified only one study [Jerusalem et al., 2000], which, although of low quality, suggests that PET is clinically useful.

The fact that the available data are evolving at a rapid pace, that is, within a span of a few months, can lead to different conclusions concerning certain uses. Referring to the results of two studies identified *after* February 2001 that are of sufficient quality for our analysis [Buchmann et al., 2001; Spaepen et al., 2001] (see Appendix 9), one might note evidence, in the form of new data, that would support recognition of two uses of PET in lymphoma: 1) when restaging could affect the choice of treatment; and 2) for evaluating residual disease after treatment.

Buchmann et al.'s study [2001] compared PET with computed tomography for staging lymphoma. Discrepant results were verified by biopsy, magnetic resonance imaging or a clinical follow-up of 4 to 24 months. PET detected lymph node manifestations of lymphoma with 99.2% sensitivity (100% specificity) compared to computed tomography, which had a sensitivity of 83.2% (specificity of 99.8%).

Spaepen et al. [2001] studied the clinical utility of PET in identifying lymphomas with lymph node, extranodal, supradiaphragmatic and infradiaphragmatic manifestations. PET was superior to computed tomography in all cases, and its sensitivity in detecting extranodal manifestations was 100% versus 80.8% for computed tomography (specificity 99.4% for both). These authors also examined the diagnostic accuracy of PET in posttreatment follow-up and showed that PET predicted persistent disease in 14/26 cases in which the results were positive.

A study of lesser quality (grade C) [Hueltenschmidt et al., 2001] confirms that PET is more specific for restaging (95% sensitivity and 89% specificity for PET vs. 95% and 39%, respectively, for conventional imaging) and for detecting recurrence (91% sensitivity and 71% specificity for PET vs. 91% sensitivity for conventional imaging, with the latter's specificity not mentioned).

Although it is outside the limits that we set for selecting studies (1999 to February 2001), this update supports the HCFA's and BCBSA-TEC's conclusions with new data. The clinical utility of PET in initial staging and posttreatment follow-up is therefore recognized.

- **Monitoring response to therapy**

✿	The MHTAC is the only organization that mentions this use for PET. The ARQ recognizes PET's potential for this application, and the CMI recognizes this use. The HCFA does not cover PET for monitoring response to therapy

No new studies on monitoring response to therapy in lymphoma were identified. At present, this is a potential use of PET.

4.1.5.4 Conclusions

In Hodgkin's and non-Hodgkin's lymphoma, the clinical utility of PET

is recognized for:

- initial staging when restaging could affect the choice of treatment; and
- evaluating residual disease after treatment;

and has potential for:

- evaluating response to therapy.

4.1.6 Breast cancer

4.1.6.1 General data

It is estimated that 19,500 Canadian women will be diagnosed with breast cancer in 2001, with 5,000 new cases in Québec. The number of deaths due to breast cancer in all the provinces in 2001 is estimated at 5,500, with 1,450 of these deaths occurring in Québec [NCIC, Canadian Cancer Statistics, 2001].

When a clinical examination in conjunction with mammography and aspiration cytology (triple approach) does not permit a definitive diagnosis, invasive procedures need to be considered. It is important to note that, in patients with an abnormal mammogram who have undergone surgery, the masses that are operated on are malignant in only 2 to 4 cases in 10. In addition, about 10% of breast cancers are not identified by mammography, even when they are palpable. This is why the diagnosis should be made on the basis of the morphological results obtained by aspiration, needle biopsy or even open biopsy [Avril et al., 2000a].

4.1.6.2 The role of PET

In breast cancer, the following uses were examined: detecting the primary tumor, staging primary and recurrent tumors, and monitoring response to therapy.

PET cannot be used as a routine test for detecting breast cancer because of its low sensitivity or because its sensitivity is comparable to that of mammography and scintimammography, which are less expensive procedures. However, it is suggested that PET could be of significant value in clinical cases that are considered difficult, especially in women with large breasts or fibrocystic disease, those who have had a first biopsy, surgery or radiation therapy, and those with breast implants. PET is also useful in evaluating an axillary mass suspected of being breast cancer and can even avoid axillary dissection. It is superior to cartography in detecting osteolytic bone metastases, although it can miss certain osteoblastic lesions. It can also prove useful in detecting recurrent or metastatic tumors and very useful in monitoring response to therapy, since it can be performed earlier than the other methods for evaluating treatment [Avril et al., 2000a; Laplante, 2000; Létourneau, 2000].

4.1.6.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Detecting the primary tumor**

✿	Although the AHTAA and BCBSA-TEC consider that there is no evidence to support PET for this use, the VA-TAP recognizes PET's potential for this application. None of the other organizations mention this use, but the AMSMNQ, the CMI and the FMSQ's PTC have all stressed its importance in clinical cases that are considered difficult.

The MSAC does not mention breast cancer in its March 2000 report. It states that there are several other potentially important uses of PET that were not examined in its report and stresses that it should not be assumed that PET has no role to play in the uses that are not mentioned in its assessment.

The HCFA did not make a PET coverage decision for breast cancer but instead referred the matter for consideration to the MCAC Diagnostic Imaging Panel.

The BCBSA-TEC states that the medical literature is incomplete when it comes to supporting the use of PET in breast cancer.

Up to February 2001, no new studies, with sufficiently convincing data, of the use of PET in breast cancer were identified.

PET has potential clinical utility in detecting primary breast cancer tumors in cases considered difficult.

- **Staging primary and recurrent tumors**

✿	Three assessment agencies (AHTAA, VA-TAP and INAHTA) recognize PET's potential for this application, especially for recurrent tumors.

Up to February 2001, no new studies of PET for the detection of breast cancer metastases were identified. This is therefore a potential use of PET.

- **Monitoring response to therapy**

✿	The MHTAC and VA-TAP recognize PET's potential for this use.

Up to February 2001, no new studies, with sufficiently convincing data, of this use of PET in breast cancer were identified. This is therefore a potential use of PET.

4.1.6.4 Conclusions

In breast cancer, PET's clinical utility is not clearly recognized, but

it has potential for:

- staging primary and recurrent tumors;
- detecting axillary and internal mammary lymph node metastases;
- detecting the primary tumor in the context of an equivocal complete evaluation; and
- monitoring response to therapy.

4.1.7 Prostate cancer

4.1.7.1 General data

It is estimated that there will be 17,800 new cases and 4,300 deaths in Canada in 2001, with an estimated 3,800 new cases and 890 deaths in Québec. (NCIC, Canadian Cancer Statistics, 2001]. It should be noted that autopsy results have shown that prostate cancer is present in about 30% of men aged 50 and in about 60 to 70% of men aged 70, but that this type of cancer presents clinical manifestations in only one third of cases [Avril et al., 2000b].

Although different schools of thought have questioned the different approaches, the diagnosis of prostate cancer is based primarily on a digital rectal examination, transrectal ultrasound (TRUS), a prostate-specific antigen (PSA) assay and a prostate biopsy. A PSA assay does not enable one to distinguish between organ-confined and more advanced disease. TRUS permits visualization of the internal architecture and entire contour of the prostate and is an important tool in staging the disease [Avril et al., 2000b].

Computed tomography and magnetic resonance imaging (MRI) are also used to evaluate the prostate. However, computed tomography does not allow one to distinguish between prostate cancer and benign hyperplasia or normal prostatic tissue. Studies have shown that MRI cannot provide adequate information for visualizing the anterior margin of the prostate. Technological developments in magnetic resonance imaging have improved its capacity to visualize the prostate, but 35 to 52% of prostate cancers go undetected by magnetic resonance imaging [Avril et al., 2000b].

4.1.7.2 The role of PET

In prostate cancer, the following use was examined: detecting recurrence or residual tumors.

It has been shown that FDG-PET has too low a detection rate to identify prostate cancer, and there is no evidence that staging regional and distant metastases and detecting recurrent cancer can be achieved with sufficient accuracy by PET. Presently, there are no hard data in favour of PET scanning in patients with prostate cancer [Avril et al., 2000b].

The members of the FMSQ's PTC consider that FDG has a limited ability to detect primary carcinoma of prostate and to differentiate between a malignant tumor and benign prostatic hyperplasia [Laplante, 2000]. However, the use of PET with other radiotracers, such as [^{11}C]-acetate, seems promising for the detection of prostate cancer [Avril et al., 2000b]. Further studies are necessary.

4.1.7.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Detecting recurrence or residual tumor**

✿	Only the MHTAC mentions PET's potential in prostate cancer.

Only one recent study of the use of PET in prostate cancer was identified [Seltzer et al., 1999], and its methodological quality is rather low (grade C; see Appendix 9). This study involved 45 patients with an elevated PSA after local curative-intent therapy (prostatectomy, radiation therapy and cryosurgery). The results of the whole-body PET scan were compared with those of the CT scan of the pelvis and abdomen in all the patients and with those of a monoclonal antibody scan in 22 of them.

The study found similar detection rates for PET and computed tomography but also showed the inferiority of the monoclonal antibody scan in patients with a markedly high PSA. The contribution of these three imaging techniques seems limited for detecting distant metastases in patients with a slightly elevated PSA, but this result might have been due to a low incidence of metastases in such cases.

The authors conclude that other studies are needed to determine the benefits of using one or more imaging modalities when choosing the appropriate treatment for patients with PSA relapse.

Since our searches identified only one inconclusive study [Seltzer et al., 1999] and since its methodological quality does not meet the selection criteria, no conclusion can be drawn in favour of the use of PET in prostate cancer. This is therefore a potential application.

4.1.7.5 Conclusions

In prostate cancer, FDG-PET has, although there are presently no data to demonstrate its efficacy, potential clinical utility in:

- detecting recurrence or residual tumors.

However, its use, as proposed in recent articles (under evaluation), is sparking keen interest.

4.1.8 Other cancers

Mention is made in the literature of PET's clinical utility in other specific situations for the following cancers, which are not discussed in detail in this report: gynecological cancers (ovarian, uterine, cervical); certain genitourinary cancers (testicles, metastases from hypernephromas); mesotheliomas; soft-tissue sarcomas; thyroid cancer; and esophageal and pancreatic cancer.

4.1.9 Review of the positions published before or in 2000 (oncology)

Current and potential users of PET in Québec feel that this technology would provide greater diagnostic accuracy than the current conventional imaging by x-ray, ultrasound or magnetic resonance. They foresee a significant technological delay, which could result in inequities between the care provided to patients in Québec and that provided in other industrialized countries if PET is not deployed in Québec [AMSMNQ, 2000; ARQ, 2000].

However, research is necessary to reinforce several aspects of the use of this technology, namely, finding new uses; lowering equipment costs; improving PET camera resolution; improving software performance; increasing the number of radioisotope distribution centres; conducting new studies of PET's validity; and broadening the use of modified PET scanners [MHTAC, 2000].

Although the evidence concerning PET's clinical efficacy and cost-effectiveness in oncology is insufficient to recommend *unrestricted* coverage of PET by various health-care programs (e.g., Medicare, BCBSA, VA-TAP), the evidence regarding its safety and its potential clinical efficacy and potential cost-effectiveness do permit the recommendation of *interim* coverage in certain clinical situations. The MSAC states that, although it has been shown that PET often leads to a change in management, it is not always clear how this will impact the clinical outcome. It points out the assumed relationship between a test's diagnostic accuracy and its results on health outcomes is not restricted to PET and that there is seldom any evidence on the effects of diagnostic tests on health. It concludes that "[t]here is no direct evidence available at this time that can demonstrate that improvements in diagnostic accuracy provided by PET, and any subsequent management changes, lead to improvements in health outcomes for patients" [Ghersi et al., 2000].

Various conditions govern the different terms of coverage. For example, the coverage of PET by Medicare (U.S.) for diagnosis and staging in several areas of oncology is subject to specific conditions of acceptance: coverage is authorized only if the PET scan results obviate the need for an invasive diagnostic procedure or permit one to accurately locate a tumor before performing an invasive diagnostic procedure. Coverage is not authorized for any other diagnostic use or for screening asymptomatic patients [Tunis et al., 2000].

4.2 NEUROLOGY

In neurology, the following uses were examined: dementia and Alzheimer's disease, refractory epilepsy and brain tumors (mainly glioma).

Although neurology was one of the first areas in which PET was used, its utilization in clinical practice has not increased at the same pace as in oncology [Couillard, 2000; Ghersi et al., 2000].

The applications of PET in clinical neurology are presently quite limited. With a few exceptions, the information provided by PET cannot be used directly to treat neurological or psychiatric diseases [Beanlands et al., 1999].

4.2.1 Dementia and Alzheimer's disease

4.2.1.1 General data

Close to 8% of Canadians aged 65 and over and close to 34% of those aged 85 and over have Alzheimer's disease or related dementia [Alzheimer's Society of Canada, 1999: www.alzheimer.ca].

Alzheimer's disease is the most common of several neurodegenerative dementias that have similar clinical manifestations. This is why there are three objectives to the diagnostic evaluation of elderly individuals with cognitive problems, namely, to determine: 1) if the patient has dementia; 2) if the clinical picture and course confirm the presence of Alzheimer's disease; and 3) if there is another primary cause of dementia or a coexisting disease (especially a cerebrovascular disease or Parkinson's disease or, less often, Pick's disease or primary progressive aphasia) that is contributing to the development of Alzheimer's disease or resulting in an atypical manifestation [Bennett, 2000a and 2000b].

The clinical diagnosis of the likelihood of Alzheimer's disease is based on many different sources of information that are considered together, since there is no single biological marker of this disease or other types of dementia (e.g., cerebrovascular and frontotemporal dementias) [Almkvist and Windblad, 1999]. There is no reliable diagnostic test for Alzheimer's disease, although certain blood and cerebrospinal fluid tests and neurological imaging procedures are currently being researched [Bennett, 2000a and 2000b].

4.2.1.2 The role of PET

Various diseases can cause dementia, memory loss and symptoms similar to those of Alzheimer's disease, for which there is no treatment. PET can be used to confirm the degenerative process associated with this disease before the onset of conclusive clinical symptoms and to make a differential diagnosis between Alzheimer's disease and diseases that are treatable or reversible. Early diagnosis enables patients and their families to plan the patient's environment and provide the necessary home maintenance resources. Psychosocial techniques and pharmacologic treatments for slowing the progression of the disease are now available and can improve these patients' quality of life [Adams et al., 1999; AMSMNQ, 2000].

Despite the lack of therapeutic modalities for this disease, PET might possibly play a role in the differential diagnosis of dementia and other cognitive diseases (e.g., Parkinson's disease).

4.2.1.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Diagnostic**

✿/✿	The HCFA recognizes PET's potential for this use. The VA-TAP, AHTAA and INAHTA recognize this potential as well but point out that, since there is no treatment for this disease, it is unlikely for PET to have any diagnostic value in this application.

The HCFA referred the matter of PET and Alzheimer's disease to the Medical Coverage Advisory Committee (MCAC) Diagnostic Imaging Panel in 2000. For the time being, the use of PET for diagnosing this disease is not covered [Tunis et al., 2000].

In the 1998 update of its 1996 report, the Veterans Affairs Technology Assessment Program (VA-TAP) concludes that "[t]he value of improved diagnostic information to AD patients and their families should not be dismissed; however, this value should be quantified in the context of accessibility and accuracy of alternative imaging technologies and of phenotypically or genetically defined subsets of AD. In the absence of effective treatments for AD, an accurate diagnostic test may be needed primarily in research for epidemiologic studies and evaluations of potential therapies" [Flynn and Adams, 1998].

Between the publication of the VA-TAP report and February 2001, two new studies were identified. One of them [Reiman et al., 2001] involved only four patients. The other [Kawano et al., 2001] examined the relationship between various IQ tests and the Mini-Mental State Examination and regional cerebral FDG uptake. Neither of these studies is applicable, based on our selection criteria, and since there is no effective treatment for this disease, the use of PET to diagnose Alzheimer's disease or related dementia is not recognized.

4.2.1.5 Conclusions

In Alzheimer's disease, the clinical utility of PET is not recognized.

4.2.2 Refractory epilepsy

4.2.2.1 General data

About 1% of the general population has epilepsy. It affects about 300,000 Canadians, and each year 1 Canadian in 2,000 is diagnosed with it, which translates into approximately 14,000 new cases per year [Epilepsy Canada, 1998: http://www.epilepsy.ca/eng/mainSet.

html].

Twenty to 30% of epileptics are refractory to antiepileptic therapy [Leung et al., 1999]. The most frequent type of refractory epilepsy is the partial complex seizure, which, in most cases, originates in the temporal lobe (temporal lobe epilepsy). For patients whose epilepsy is refractory to the usual treatments, surgery may lead to complete or partial seizure control. The choice of surgical treatment depends on the exact location of the epileptogenic focus [Leung et al., 1999].

It has been suggested that more than 200,000 epileptics in the United States could benefit from surgical treatment, but the need to perform numerous, complex preoperative tests (e.g., using conventional imaging [ictal and interictal], various invasive methods and EEG) greatly limits these interventions [Devous et al., 1998].

The cognitive and psychosocial sequelae of constant epileptic seizures in a child should be considered differently from those occurring in adults because they can lead to developmental and growth stagnation. For each individual child, the potential risk/benefit ratio for surgery should be carefully weighed. Some studies have shown that delaying surgery for childhood-onset epilepsy until adulthood can lead to significant psychosocial, behavioural and educational problems [Wyllie, 1998].

4.2.2.2 The role of PET

The advantage of interictal PET over other diagnostic modalities is that it can be performed between seizures, unlike ictal digital SPECT, for example, which must be performed several times. In addition, PET can reveal areas of cortical dysplasia that cannot be visualized with magnetic resonance imaging, delineate the area of epileptic dysfunction in conjunction with EEG and digital SPECT, substitute for preoperative functional localization tests, especially in pediatric patients, and be used for the preoperative evaluation [Carmant, 2000]. Furthermore, the combined use of PET and MRI permits the precise localization of epileptogenic foci and obviates the need for invasive monitoring by deep electrodes, a labour-intensive and expensive procedure whose results are difficult to interpret [AMSMNQ, 2000].

4.2.2.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

- **Determining the location of epileptogenic foci**

✿/✿	The HCFA, MSAC and BCBSA-TEC recommend coverage of PET for this use. The AHTAA also recognizes the utility of PET in such cases, while the INAHTA concludes that the quality of the efficacy evidence for interictal PET in epilepsy is lacking.

The authors of the MSAC report base their conclusion concerning the clinical utility of PET for localizing epileptogenic foci in epilepsy on five studies [Swartz et al., 1992, 37 patients; Ferrie et al., 1996, 32 patients; Delbeke et al., 1996, 38 patients; Chee et al., 1993, 40 patients; and Markand et al., 1997, 67 patients]. The authors state that the sensitivity was relatively high but mention certain problems that should be taken into consideration, such as reference standards based on a combination of tests; the fact that the surgical outcome was used to measure the accuracy of PET (only patients with positive PET results underwent surgery, which results in 100% sensitivity); and patient selection (most studies selected patients who had undergone surgery). The authors did not provide any information on the patients who had undergone a presurgical workup but who were not operated on, which would have included patients who may have had a negative result if they had had a PET scan, etc. [Ghersi et al., 2000].

The Australian report nonetheless states that "[it] is reasonable to conclude that a subset of patients who would be helped by surgery will benefit as a result of a positive PET scan. It is unclear how much PET is helping all patients with refractory epilepsy, because we lack information regarding false-negative PET results...and patients testing positive by PET but not undergoing surgery." The authors nevertheless recommend interim coverage of PET for evaluating patients with refractory epilepsy who are being considered for surgery in the context of a comprehensive epilepsy program, where localization based on a standard assessment, including EEG, MRI and semiology, is inconclusive.

The HCFA bases itself on a study that the Australians used as well [Delbeke et al., 1996]. The study showed that PET had a high positive predictive value for postsurgical improvement (94%). The PET and EEG findings were concordant in 86% of the cases. The authors of the study concludes that, in terms of health outcomes, the impact of PET's diagnostic accuracy would be the ability to quantify postsurgical outcomes more accurately [Tunis et al., 2000].

To underscore this positive impact on morbidity and quality of life, the HCFA also mentions the study by Engel et al. [1990], who report that some patients may have avoided an invasive EEG (and other, noninvasive tests), thanks to localization of the epileptogenic focus by PET.

Three studies between 1999 and February 2001 were identified [Dupont et al., 2000; Muzik et al., 2000; and Hwang et al., 2001]. Of these three studies, only that by Hwang et al. [2001] compared FDG-PET with conventional imaging.

Hwang et al.'s study [2001], which involved 117 patients (grade B), compared PET with interictal SPECT, ictal SPECT and MRI. It showed that PET can localize epileptogenic foci with 77.7% accuracy versus 59.8% for MRI and 70.3% for ictal SPECT (concordance rate between the three modalities: 38%). The accuracy rate for the localization of neocortical epileptogenic foci was 86.7% for PET, with 64% and 80.6% for MRI and ictal SPECT, respectively. PET localized extratemporal epileptic foci with 70.7% accuracy, which was better than MRI and SPECT (56.7% and 63.6%, respectively). The authors found that PET was the most sensitive of the three methods in detecting each substrate of epilepsy and that MRI was as sensitive as PET in detecting tumors causing certain epilepsies and the least sensitive in detecting neuronal migration disorder.

They also discuss the impact of imaging on the health of individuals with refractory epilepsy, reporting good surgical outcomes in 81.4% of the patients with imaging abnormalities (compared to 59.5% for those without imaging abnormalities). The authors conclude that PET and ictal SPECT are generally more sensitive than MRI (despite the low concordance rate between the two tests and variable sensitivity that depended on the substrate), that the detection of abnormalities by MRI is associated with favourable outcomes and that PET and ictal SPECT can be used in a complementary fashion, especially when the MRI is negative.

Hwang et al.'s [2001] study supports the conclusions of the MSAC's and HCFA's reports and provides additional data for recognizing the clinical impact that PET can have on health outcomes in individuals with refractory epilepsy while at the same time obviating the need for numerous invasive, diagnostic procedures.

4.2.2.5 Conclusions

In refractory epilepsy, the clinical utility of PET

is recognized for:

- localizing epileptogenic foci in patients with refractory epilepsy who are being considered for surgery and where inconclusive localizing information is provided by a standard assessment, including seizure semiology, EEG and MRI.

4.2.3 Brain tumors (mainly glioma)

4.2.3.1 General data

It is estimated that there will be 2,400 new cases of brain cancer and 1,550 deaths due to this disease in Canada in 2001. Québec is the Canadian province where there are the most brain tumors, with an estimated age-adjusted incidence for 2001 of 10 in 100,000 males and 7 in 100,000 females compared to an average of about 7 in 100,000 males and 4 in 100,000 females in the other provinces [NCIC, Canadian Cancer Statistics, 2001].

Although various types of tumors can occur in the brain, nearly 50% of these neoplasms derive from glial cells. The other 50% include other types of tumors, such as metastases and meningiomas, which are the most common. Gliomas are the only brain tumors that have been evaluated in detail by PET [Kuwert and Delbeke, 2000].

Magnetic resonance imaging and computed tomography are the two most commonly used imaging techniques for the detection and differential diagnosis of brain lesions, but in some cases, they are unable to distinguish between neoplastic and nonneoplastic processes. It can also be difficult, with these diagnostic methods, to differentiate between a low-grade glioma and chronic inflammation or between a high-grade brain tumor and certain benign processes, such as toxoplasmosis or a hemorrhagic infarction [Kuwert and Delbeke, 2000].

The staging of brain tumors is based on tumor contrast, which can be accomplished by computed tomography or magnetic resonance imaging [Kuwert and Delbeke, 2000].

4.2.3.2 The role of PET

In glioma, the following uses were examined: evaluating the malignant transformation of a low-grade glioma, preoperative workup, determining the histology of the tumor, choice of treatment, prognosis, detecting metastases, posttreatment follow-up (differentiating between radionecrosis and recurrence).

FDG-PET is not suitable for differentiating a low-grade glioma from a benign process, since low-grade gliomas do not take up FDG. FDG-PET can, however, be used for correctly differentiating a high-grade glioma from nonneoplastic processes, since such gliomas exhibit high FDG uptake. FDG-PET can also differentiate, for example, between a hemorrhagic infarction and a malignant astrocytoma [Kuwert and Delbeke, 2000].

FDG-PET is often used as a complement to magnetic resonance imaging, and, in certain cases, the correlation between PET images and amplified MRI images is crucial for differentiating between FDG uptake by high-grade tumors and its uptake by normal cortex. False-positive results can occur in patients with grade I gliomas and certain low-grade oligodendrogliomas, which exhibit high FDG uptake

[Couillard, 2000; Kuwert and Delbeke, 2000].

The level of FDG accumulation in gliomas is indicative of the degree of malignancy. PET can therefore be used both for staging brain tumors and for guiding the biopsy toward the most undifferentiated region (maximum metabolic activity). PET-guided biopsy increases diagnostic accuracy to nearly 100% [Kuwert and Delbeke, 2000].

During follow-up, computed tomography and magnetic resonance imaging cannot always differentiate between radionecrosis and recurrent tumors. PET is an important tool for follow-up purposes, since high-grade tumors exhibit higher FDG uptake than radionecrosis. However, the clinical utility of PET in detecting recurrence is not always reliable, for the more aggressive the radiation therapy, the lower the diagnostic efficacy. Since low-grade gliomas do not accumulate FDG, functional imaging with radiolabelled amino acids is one of the only modalities—with digital SPECT—that can detect a recurrent low-grade glioma [Couillard, 2000; Kuwert and Delbeke, 2000].

At present, functional imaging with PET cannot substitute for computed tomography or magnetic resonance imaging but does provide additional information that cannot be obtained by morphological imaging alone [Kuwert and Delbeke, 2000].

4.2.3.3 Previous positions and update

The list below is based on the positions (conclusions and decisions) of organizations that used explicit assessment criteria. In practice, of the more recent reports, those of the MSAC and HCFA are cited first. Expert opinions are included to shed further light on the subject, if need be. A complete list of the positions is provided in Appendix 7. The studies selected and evaluated for the updates using the criteria set out in Chapter 3 and in Appendix 6 are presented in Appendix 8.

The MSAC mentions several potential uses of PET in glioma. However, it limited its assessment to differentiating between radionecrosis and recurrent glioma, based on a retrospective audit of clinical records by Deshmukh et al. [1996, 75 patients], who found that 87% of the PET scans between September 1990 and June 1992 in cases of glioma were for the purpose of differentiating between radionecrosis and tumor recurrence [Ghersi et al., 2000].

- **Evaluating the malignant transformation of a low-grade glioma**

✿	The MSAC, MHTAC and INAHTA recognize PET's potential for this application.

Four new studies [De Witte et al., 2001; Eary et al., 1999; Derlon et al. 2000; and Roelcke et al., 1999] were identified, but all are methodologically flawed. De Witte et al. [2001] conclude that FDG-PET is not superior to pathologic grading for predicting survival. Eary et al. [1999], Derlon et al. [2000] and Roelcke et al. [1999] compared FDG-PET with C-11 methionine (MET) PET. Their findings were concordant. Results with FDG-PET were inferior to those with MET PET, which sharply delineated the tumors in most of the cases. Despite the poor quality of these studies, these results indicate that C-11 methionine PET has a potential role in identifying tumors progressing to malignancy.

Since this update did not uncover any robust evidence, this use of PET is a potential application.

- **Preoperative workup**

✿	The MSAC and INAHTA state that PET has potential for this use.

No new studies were identified. This use of PET is a potential application.

- **Grading tumors**

✿/✿	The MSAC and INAHTA mention this use and recognize PET's potential for it. In the MHTAC's opinion, there are no hard data in favour of PET for this application.

No new studies were identified. This use of PET is a potential application.

- **Choice of treatment**

✿	The MSAC, MHTAC and INAHTA mention PET's potential in the management of patients with brain tumors.

A single study (grade C) was identified. Nuutinen et al. [2000] studied the impact of C-11 methionine PET on the planning of the management of patients with low-grade astrocytomas. Their results suggest that this modality was helpful in choosing the treatment in only 27% of the patients, whereas PET used in combination with MRI was helpful in 46% of the patients. This update does not permit recognition of this use of PET, which remains a potential application.

- **Prognosis**

✿	Only the MSAC mentions this use and recognizes PET's potential in this regard.

Up to February 2001, two studies on determining the prognosis of glioma by PET were identified. One of them [De Witte et al., 2001], although of poor quality, did not demonstrate PET's superiority to the pathologic examination in grading brain tumors. The other [Nuutinen et al., 2000], also a grade C study, suggests a strong association between MET-PET and the prediction of survival in patients with a standardized uptake value greater than 3.5. Since these results are not convincing, this remains a potential application of PET.

- **Detecting metastases**

✿	The MHTAC and INAHTA mention PET's potential for this application.

No new studies were identified. This is a potential use of PET.

- **Posttreatment follow-up: differentiating between radionecrosis and recurrence**

✿/✿	The AHTAA and MSAC support the use of PET for this use. All the potential users consider that PET has clinical utility in this application. The MHTAC and INAHTA recognize its potential for this use.

Although the MSAC based its conclusions concerning the use of PET for evaluating gliomas on 16 studies, the authors state that there are too few data to draw any firm conclusions as to the superiority of PET to SPECT with regard to differentiating radionecrosis from recurrent tumor. In addition, the studies of the diagnostic accuracy of PET vary widely from a methodological standpoint. None of the studies examined in the Australian report for the purpose of making a coverage recommendation concerning the differentiation of radionecrosis from recurrent glioma in patients who have received radiation therapy and who have residual structural abnormalities on diagnostic imaging clearly demonstrated PET's superiority. Furthermore, the Australian report cites a study by Bader et al. [1999, 30 patients], which, although limited by a small patient sample, seems to suggest that FDG-PET's efficacy in distinguishing between radionecrosis and recurrence varies considerably according to the grade of the glioma.

Bader et al. [1999] compared the efficacy of FDG-PET and that of I-123 SPECT in detecting and grading recurrence in patients previously treated for glioma. Based on the histopathological data, SPECT and PET findings confirmed recurrence in all the cases of high-grade (IV) gliomas. However, for grade II and III gliomas, PET was inferior to SPECT, with true-positive results in 71% of the cases of grade III and 50% of the cases of grade II tumors compared to 86% (grade III) and 75% (grade II) for SPECT. The authors conclude that grading brain tumors by PET is hindered by problems confirming the malignant progression of a grade II glioma to a grade III or IV glioma. Nonetheless, in all, FDG-PET confirmed an upgrading in 75% of the cases.

The MSAC also cites a retrospective audit of clinical records by Deshmukh et al. [1996], which showed that PET had a positive impact on the clinical management of patients. The authors of this report state that little is known about the effects of PET on the health of patients with recurrent glioma, but that it would be reasonable to expect improvements in their health in terms of morbidity, mortality and quality of life. Deshmukh et al. [1996] found that the FDG-PET findings led to the consideration of a new therapy in 31% of the cases, including the decision to initiate chemotherapy in 21% of the cases and surgery in 10% of the cases, with a biopsy in only 2/89 cases and surgical resection in 7/89 cases. The PET findings also contributed to a decision to withhold aggressive therapy in 59% of the cases: chemotherapy in 15% of the cases, surgery in 7% of the cases, radiosurgery in only 2/89 cases and unspecified "aggressive action" in 36% of the cases. These decisions were made in light of PET results only in 28% of the cases and of PET results supported by other information in 72% of the cases. In general, the authors conclude that PET played a valuable clinical role in 86 of the 89 cases.

Despite the methodological weaknesses, which reduce the convincingness of the available data, the MSAC recommends that PET be funded on an *interim* basis for the differentiation of radionecrosis from tumor recurrence in patients treated with radiation therapy who have residual structural abnormalities on diagnostic imaging [Ghersi et al., 2000].

Our searches did not reveal any new studies on differentiating between radionecrosis and recurrence. The MSAC's conclusion is stated here: This use is recognized until such time as new data confirm or invalidate this conclusion.

4.2.3.5 Conclusions

In brain tumors (mainly gliomas), the clinical utility of PET is

recognized for:

- evaluating residual lesions after treatment of a recurrent glioma and differentiating between radionecrosis and recurrence in patients treated with radiation therapy who have abnormalities on diagnostic imaging;

and has potential for:

- the initial staging of patients suspected of having a primary brain tumor, in order to guide biopsy to the highest area of activity;
- evaluating the progression of a low-grade glioma to malignancy;
- the preoperative workup;
- grading tumors;
- the choice of treatment;
- determining the prognosis; and
- detecting metastases.

4.2.4 Other clinical uses in neurology and psychiatry

Other avenues of application in neurology and psychiatry are mentioned in the literature, but they are not examined in detail in this study.

They include Parkinson's disease, neurological pain, multiple sclerosis, language problems and schizophrenia.

4.2.5 Review of positions published in or before 2000 (neurology)

The need for PET in the field of neurology is presently quite limited because the specific information that it provides cannot, at this time, be used for therapeutic purposes, with a few exceptions. However, knowledge in this field is evolving, which could lead to a rapid increase in the demand for PET. This is why the strategy concerning the use of PET in neurology should be one of close observation, including the integration of limited applications at existing PET centres. The CMI recommends that the need for PET in neurology be monitored closely and that services be made available at certain tertiary care centres for validated neurological applications [CMI: Beanlands, 1999].

In light of the available data, the INAHTA recognizes PET's contribution to our knowledge of the biochemical and physiological mechanisms of several cerebrovascular and neuropsychiatric diseases but does not conclude that the information provided by PET can or cannot improve patient management or final health outcomes. The available evidence is based on small, methodologically flawed studies.

The clinical indications for PET in neuropsychiatry have been under investigation since the early 1980s, and after two decades, questions about its clinical utility persist and are limiting its diffusion in clinical practice. Furthermore, PET's diagnostic value in a number of neurological applications has been called into question because there is no treatment for improving the prognosis of certain diseases, e.g., Alzheimer's dementia [INAHTA: Adams et al., 1999].

4.3 CARDIOLOGY

The research methodology used was explained above (Chapter 3 and Appendix 6). Briefly, it consists of a synthesis of the available assessment reports and an update of the recent literature published on the subject

4.3.1 General data

4.3.1.1 The pathophysiology of myocardial impairment

Viable myocardium is that which still has the ability to contract. Viable myocardium can be normal, stunned (postischemic contractile dysfunction) or hibernating (persistent but potentially reversible deterioration of myocardial function). Briefly, myocardial stunning is a reversible state of regional contractile dysfunction that occurs after an ischemic episode, even in the absence of myocardial necrosis. It can be an acute ischemic episode or repeated ischemic episodes, symptomatic or nonsymptomatic, in a patient with one or more coronary stenoses. Resting myocardial blood flow may be relatively normal. On the other hand, myocardial hibernation is a state of potentially reversible chronic ventricular dysfunction associated with permanent, inadequate blood supply. These two terms describe different pathophysiological processes. However, in clinical practice, the dividing line between the two states is not always clear.

○ ***Why evaluate myocardial viability?***

Several studies have shown that revascularization techniques (bypass and angioplasty) improve global and regional ventricular dysfunction in coronary patients [Rees et al., 1971; Chatterjee et al., 1973; Brundage et al., 1984; Braunwald et al., 1986; Rahimtoola, 1989; Van den Berg et al., 1990; Elefteriades et al., 1993; and Vanoverschelde et al., 1997], which improves quality of life, reduces the occurrence of cardiac events and can prolong life expectancy. Thus, it is estimated that the left ventricular ejection fraction (LVEF) can improve significantly after revascularization in 25 to 40% of coronary patients with global left ventricular dysfunction [Bonow et al., 1996].

In patients with coronary ischemia and more or less preserved left ventricular function, myocardial revascularization, if indicated, involves a small surgical risk [Kennedy et al., 1981]. However, in patients with severe left ventricular dysfunction (LVEF ≤ 35%), revascularization provides little or no benefit if the myocardial tissue is not viable. The mortality rate associated with bypass surgery in such patients is 5 to 37% [Zubiate et al., 1977; Hellman et al., 1980; Hochberg et al., 1983; Marwick et al., 1995]. It is for this category of patients that studying myocardial viability is so important [Bax et al., 1998], for it is this population that benefits the most from revascularization in the presence of viable myocardium [Yusuf et al., 1994]. Patients with low myocardial viability, as evaluated preoperatively, have a poorer prognosis than those who have better viability [Pagley et al., 1997; Pasquet, 1999]. Patients with nonviable myocardium do not benefit from revascularization and must be treated pharmacologically or undergo transplantation. However, in patients in whom transplantation is considered and in whom a sufficient quantity of viable myocardium has been detected, the strategy should be modified in favour of myocardial revascularization. By identifying patients with viable myocardium, the therapeutic options (medical, revascularization or transplantation) will be optimized and the prognosis improved accordingly.

In Québec, 6,000 to 7,000 coronary bypasses and 9,000 to 10,000 angioplasties are performed each year, increasingly in patients with severe left ventricular dysfunction. These bypasses and angioplasties cost $100 million a year. To ensure optimal resource utilization, patients who are to undergo revascularization procedures should be properly selected. The detection of myocardial viability is a determining factor in the process of identifying these patients, especially those with severe left ventricular dysfunction.

4.3.2 The role of PET in cardiology

PET can be used to characterize and quantify the different functions of cardiac tissue. Its use in research has provided new information about cardiac physiology and pathophysiology [Camici, 2000].

The isotopes most widely used in cardiology are listed in the table below, together with their half-lives, the parameters they measure and their source of production. Because of the very short half-life of most of the radiotracers used in cardiology, the use of PET in this field requires a cyclotron on the same site as the scanner.

Table 2: Radiopharmaceutical tracers used most often for PET in cardiology

[Pirich and Schwaiger, 2000]

ISOTOPE	RADIOPHARMACEUTICAL	HALF-LIFE	PARAMETER MEASURED	SOURCE
Rb-82	Rubidium	76 sec	Blood flow	Generator
O-15	Oxygen	2 min	Blood flow	Cyclotron
N-13	Ammonia	10 min	Blood flow	Cyclotron
C-11	Acetate	20 min	Oxidative metabolism/	Cyclotron

			perfusion	
F-18	Deoxyglucose	109 min	Metabolism	Cyclotron

4.3.2.1 Myocardial perfusion studies

Oxygen-15-labelled water and N-13 ammonia are the most widely used radiopharmaceutical tracers for quantifying regional myocardial perfusion by PET. One can also use rubidium-82 or Cu-62-PTSM (copper-62-pyruvaldehydeII bis(N4-methyl)thiosemicarbazone). Unlike FDG, these tracers have a very short half-life (from a few seconds to a few minutes). As a result, a cyclotron is required on the premises where they are used. Presently, coronary angiography is the gold standard for studying myocardial perfusion. Myocardial perfusion can also be studied with single-photon emission computed tomography (thallium-201 or technetium-99m-sestamibi). The advantage of PET over SPECT is that it enables one to quantify different parameters and accurately correct for the photon attenuation caused by soft tissues, which sometimes make the scans difficult to interpret (obesity, mammary or diaphragmatic attenuation).

PET can also be used to study coronary vasodilation reserve (study of coronary microvascular function). Quantifying this reserve is useful in evaluating the functional significance of coronary stenoses.

Perfusion studies have other potential uses, but they have yet to be validated: follow-up on the effects of angioplasty or cholesterol-lowering agents, the postbypass evaluation of blood flow in transplants, the detection of restenoses, and posttransplant evaluation.

4.3.2.2 Study of the metabolism of free fatty acids, glucose and oxygen

Myocardial glucose uptake can be assessed with PET and the glucose analog 18-fluorodeoxyglucose (FDG). Glucose plays a key role in metabolism in ischemic myocardium. In normal myocardium, fatty acids are the primary energy substrate for the myocytes' energy metabolism, but in ischemic myocardium, glucose becomes their primary energy source. Glucose uptake can be measured with FDG, which is transported across the membrane in the same manner. In ischemic and hypoxic myocardium, FDG competes with glucose. It is phosphorylated to FDG-6-phosphate by an enzyme, hexokinase, and cannot subsequently be dephosphorylated or metabolized. It therefore remains trapped in the myocardium. FDG uptake is increased or preserved in several altered states of the myocardium associated with contractile dysfunction and/or reduced perfusion, which indicates persistence of metabolic activity and therefore residual viability with a potential for recovery after revascularization.

Increased or preserved FDG uptake has been observed during ischemia, postischemic myocardial stunning and myocardial hibernation.

4.3.2.3 Detection of myocardial viability

There are several methods for studying myocardial viability. They include nuclear imaging techniques, such as late redistribution thallium-201 imaging after rest injection, resting technetium-99m perfusion imaging, ^{18}F-FDG-SPECT and ^{18}F-FDG-PET. Dobutamine stress echocardiography is widely used as well, and it has also been proposed that nuclear magnetic resonance imaging could be used.

Viable myocardium can exhibit normal or diminished coronary blood flow [Haas et al., 1997]. If resting metabolism is preserved, glucose utilization may be normal or increased. The presence of viable myocardium can be detected by evaluating both coronary blood flow and metabolism.

PET scans (perfusion/metabolism) can yield three possible results:

1. Normal coronary blood flow and normal FDG uptake.
2. Reduced blood perfusion and preserved or increased FDG uptake (perfusion/metabolism mismatch).
3. A proportional reduction in blood flow and FDG uptake (perfusion/metabolism match).

Areas of the myocardium where there is concordance between reduced blood flow (measured by means of N-13 ammonia, O-15-labelled water or rubidium-82) and decreased glucose utilization (measured by FDG uptake) are nonviable infarcted areas. However, if there is decreased myocardial blood flow with preserved FDG uptake, the myocardium is considered viable. Thus, scenario 2 depicts a potential for reversible myocardial dysfunction (viable myocardium), while scenario 3 depicts irreversible myocardial dysfunction and therefore implies infarcted areas.

4.3.2.4 Study of autonomic cardiac function

PET technology can be used to conduct unique studies of the links between the heart and nervous system [Schwaiger et al., 1990a and 1990b; Bengel et al., 1999; Stevens et al., 1999, Tamaki, 1997]. For example, one can study cardiac innervation with specific neuronal tracers, pre- and postsynaptic circuits, and the number, density, location and quality of the receptors in the autonomic nervous system [Wieland et al., 1990; Goldstein et al., 1990; Allman et al., 1993; Calkins et al., 1993a and 1993b; Lefroy et al., 1993; Schafers et al., 1998a and 1998b; Merlet et al., 1993; Choudhury et al., 1996; Law et al., 2000]. The nature of the interactions between the sympathetic and parasympathetic nervous systems and the relationship between innervation and the regulation of coronary blood flow can be studied as well [Di Carli et al., 1997; Stevens et al., 1998a]. These imaging and neurocardiac characterization methods, which are presently unique to PET, are expanding our knowledge of the pathophysiology of heart failure [Goldstein et al., 1990; Merlet et al., 1993]; cardiac transplantation [Di Carli et al., 1997, Stevens et al., 1998a]; dilated [Merlet et al., 1993] and restrictive and hypertrophic [Lefroy et al., 1993; Schafers et al., 1998a; Choudhury et al., 1996] cardiomyopathies; myocardial infarction [Allman et al., 1993]; diabetic cardiomyopathy [Stevens et al., 1998a and 1998b]; severe cardiac rhythm disturbances [Calkins et al., 1993a; Schafers et al., 1998b]; and sudden death [Calkins et al., 1993b]. The tracers used are ^{11}C-hydroxyephedrine (^{11}C-HED), a norepinephrine analog [Di Carli et al., 1997]); [^{11}C](S)-CGP 12177, a nonselective beta-antagonist employed in postsynaptic studies; [^{11}C]GB67, which is used to study alpha-1 receptors [Law et al., 2000]; and [^{11}C]m-hydroxyephedrine, which is used to study presynaptic sympathetic innervation. Presently, at least 15 or so radiotracers are being used in this area of research [Tamaki, 1997].

Another, rather new but extremely promising field is the exploration, using PET, of gene expression in cardiac physiology and pathophysiology [Gambhir et al., 1999].

4.3.2.5 Follow-up of transplanted patients

In addition to PET being used as a tool for selecting cardiac transplantation candidates, several studies have employed PET in the follow-up of transplanted patients for the purpose of evaluating regional sympathetic reinnervation of heart transplants [Bengel et al., 1999; Uberfuhr et al., 2000a; Uberfuhr et al., 2000b]. PET is also used to study posttransplant myocardial perfusion [Kushwaha et al., 1998] and the progression of atheromatous disease in grafts [Allen-Auerbach et al., 1999].

4.3.2.6 Monitoring the effect of therapeutic interventions

PET can be used to monitor coronary vasomotor response to various therapeutic interventions, whether pharmacologic or risk factor modifications [Czernin et al., 1995]. Studies have revealed, by means of PET, that risk factor modifications accompanied by healthier living results in a decrease in the severity of stress-induced myocardial perfusion abnormalities [Gould et al., 1995]. In addition, the literature contains several studies of coronary flow reserve changes during cholesterol-lowering therapy [Gould et al., 1994; Guethlin et al., 1999; Yokoyama et al., 1999; Baller et al., 1999]. PET has also been used to study myocardial perfusion under the effect of verapamil in patients with hypertrophic myocardiopathy [Choudhury et al., 1999] and to quantify endothelium-dependent coronary vasodilation during the administration of L-arginine or hormone replacement therapy [Campisi et al., 1999a; Campisi et al., 1999b].

4.3.2.7 Other uses

Other applications of PET have been proposed for studying ^{11}C-acetate metabolism in congestive heart failure and cardiac arrhythmias (^{18}F-dopamine, ^{11}C-HED).

4.3.3 Previous positions and update

A more detailed summary of the following positions is provided in Appendix 7.

The MSAC (March 2000) specifically studied the role of PET in evaluating coronary artery disease in patients with left ventricular dysfunction who, on digital SPECT, are found to have nonviable myocardium or where viability is uncertain. The MSAC concludes that there is presently not enough evidence to draw any firm conclusions regarding the clinical efficacy and cost-effectiveness of PET in this application. In most cases, PET is added to other diagnostic modalities. Further assessments of this technology are necessary. The committee recommends that FDG-PET be funded on an interim basis, on the condition that clinical and/or economic data from MSAC-approved, prospectively designed studies are provided to a central body so as to enable more long-term decisions to be made about the role of FDG-PET in clinical practice.

For the HCFA, as regards the impact of FDG-PET findings on patient health, in cases where the SPECT scan is negative and the PET scan is positive, there are insufficient literature data to state that a change in patient management would result in improved health outcomes. In cases where the SPECT scan is positive but questions remain as to the appropriateness of revascularization, PET could be a promising test, based on the literature examined. Medicare (U.S.) was already covering rubidium-82 PET for evaluating myocardial perfusion at rest or with pharmacological stress in the context of managing patients with known or strongly suspected coronary artery disease, when PET was used in place of SPECT or following a SPECT scan that was inconclusive. In December 2000, Medicare also began covering FDG-PET for evaluating myocardial viability following a positive SPECT scan, but when there is doubt as to myocardial viability if revascularization is considered. Coverage for this test in other applications was referred for study to an advisory committee consisting of nuclear imaging experts.

The INAHTA [1999] concludes that the metabolic information provided by PET may improve patient selection for revascularization and increase the chances of successful surgery. PET may offer cost savings by eliminating unnecessary angiography or revascularization in certain patients. As for evaluating myocardial perfusion, PET appears to have superior performance, but the improvement in performance in relation to digital thallium SPECT and the extent of its contribution to managing patients are not clear. PET is more expensive than other noninvasive strategies and has not yet replaced coronary angiography for assessing coronary artery disease. For patients at intermediate risk (25 to 50% probability of having either a 50% or greater left main coronary artery occlusion or a greater than 70% occlusion of an other coronary artery), PET is not a cost-effective alternative to immediate coronary angiography or other noninvasive tests, such as stress echocardiography or SPECT. There are not enough data to determine the cost-effectiveness of PET in diagnosing coronary artery disease. For determining myocardial viability and/or predicting the risk of cardiac events, most assessments have found that PET has comparable sensitivity and superior specificity to other modalities, although the studies were few in number and often lacked methodological robustness. As regards improving the likelihood of successful revascularization and cost savings, the data are insufficient to confirm that PET is favourably cost-effective. As for monitoring the effectiveness of treatment in coronary patients who have hypertension or cardiomyopathy, the evidence is insufficient. This application is still being researched.

The Alberta Heritage Foundation for Medical Research [Cowley et al., 1999] reports that PET and dobutamine stress echocardiography have the same level of diagnostic efficacy, but that the evidence is limited. There is some methodologically weak evidence pointing to the predictive value of PET as regards the clinical outcome of patients who undergo this test. In Alberta, the use of these methods to evaluate myocardial viability should be accompanied by prospective studies with a long-term patient follow-up.

The reports submitted by the FMSQ, AMSMNQ and ARQ [September 2000] note that the recognized and potential uses of PET are numerous. Accordingly, PET is the best technique for identifying ischemic but viable myocardium in patients with compromised left ventricular function and for evaluating myocardial perfusion, thus permitting better patient selection for revascularization or a heart transplant. PET is considered to be an imaging modality with an established role. The Québec population's accessibility to it should therefore be ensured, especially in cardiology. Over the next few years, frequent use will also be made of PET in cardiology research. The reports also mention the very short half-life of the radiotracers used in cardiology and call attention to the need to install cyclotrons at cardiology centres so as not to compromise the use of PET in this field.

For the CMI [1999], too, FDG-PET imaging has proven utility in evaluating myocardial viability for the purpose of selecting patients with reduced cardiac function for revascularization and candidates for a heart transplant. Similarly, according to this organization, studying myocardial perfusion with PET has proven utility in the diagnosis and prognosis of coronary artery disease; the diagnosis of coronary artery disease in the subset of patients prone to false-positive results with conventional nuclear imaging; the evaluation of the progression or regression of the disease in the context of therapeutic interventions; and the detection of a decrease in coronary reserve in patients with ischemic disease not associated with coronary atherosclerosis. The CMI recommends that when deciding on the location of PET centres, one take into account patients with heart disease as one of the two most important priorities, the other being oncology.

The tables below summarize the different positions regarding the uses that were examined.

- **Coronary perfusion**

Diagnosis, prognosis and management of coronary artery disease

✿/✿	Use recognized by the HCFA and BCBSA and considered a potential application by the INAHTA and MSAC, which include cost-effectiveness in their analyses (lack of high-level evidence).

Evaluating response to therapy

✿	Recognized use, according to potential users, and is in the process of being assessed for the INAHTA.

Detecting restenosis

NM	Use recognized by the ARQ. Not mentioned by assessment agencies, which have mainly examined myocardial viability.

Detecting diminished coronary reserve in patients with ischemia associated with noncoronary disease

NM	Use recognized by potential users but not mentioned by the other organizations.

- **Myocardial viability**

Initial evaluation and selection for revascularization

✿/✿	The HCFA recommends coverage for this use of PET if the SPECT scan is positive and there is some question as to the appropriateness of revascularization. The MSAC recommends coverage if the conventional tests for evaluating viability are negative and the patient is being considered for revascularization. For the INAHTA, PET is an effective evaluation method, but there is insufficient data to determine its cost-effectiveness. The AHFMR considers this technology effective but that its use should be accompanied by prospective studies.

Evaluating patients for a heart transplant

NM	Use recognized by potential users but not mentioned by assessment organizations.

The diversity of opinions and conclusions in the different assessment reports stems from a lack of data for drawing any firm conclusions and clearly underscores the need for further clinical research in this area.

- **Update**

We focused our assessment on the benefit of introducing PET into clinical practice for evaluating myocardial viability in patients with heart failure who are being considered for myocardial revascularization. The second use for which there is abundant literature is evaluating myocardial perfusion.

PET is more effective (sensitivity and specificity) in diagnosing coronary artery disease than single-photon emission computed tomography or stress electrocardiography [Adams et al., 1999]. Presently, the limitations of this use of PET are its high cost and low availability. Thus, although PET can provide additional quantitative information in relation to coronary angiography, the latter is the reference test for this use.

There are insufficient data to draw any firm conclusions about the cost-effectiveness of PET as a tool for diagnosing coronary artery disease. For patients with an intermediate cardiovascular risk (25 to 50% probability of having a 50% or greater left main coronary artery occlusion or a greater than 70% occlusion of any other coronary artery), Garber's meta-analysis [1999] shows that PET is not a cost-effective alternative to immediate coronary angiography or other noninvasive tests, such as stress echocardiography or SPECT, for studying myocardial perfusion. However, this meta-analysis has certain limitations. In particular, only three PET studies where considered, with no direct comparison between the different diagnostic modalities. However, other economic studies, such as Patterson's [1995], have shown that PET is the most cost-effective test in patients with a pretest probability of coronary artery disease of less than 70%.

The update was done after reviewing the literature, in order to describe the current knowledge on the basis of published data on the sensitivity and specificity of PET in detecting myocardial viability.

Most of studies that have evaluated PET have significant methodological flaws. Furthermore, there are few highly reliable data on the impact of using the technology on patient management.

Tables 33 and 34 (Appendix 8) show the two types of available studies. Table 34 presents studies that have evaluated PET using an intermediate assessment criterion, it most often being the recovery of segmental myocardial motion after revascularization, and that do not permit a true assessment of the positive clinical impact of PET. Numerous factors can explain the differences in the results of these studies [Cowley et al., 1999, Part 2]. In some of them, the calculations are based on all the dysfunctional segments, in others, only the successfully revascularized segments. In addition, the left ventricular ejection fraction varies from study to study (coronary arteries affected to varying degrees). In other studies, different protocols were used for PET scanning and for the segmental division of the ventricle.

Table 33 shows studies that used a clinical assessment criterion. Most of them were retrospective and of little power and had methodological biases. However, their results may suggest that PET has a positive impact on clinical outcomes. Nonetheless, because of the absence of comparison groups in most of the studies, one cannot be completely affirmative or, in any event, draw any conclusions.

Corroborating the results of Dreyfus et al.'s study [1994] of 46 patients, Akinboboye et al. [1999] showed, in 33 patients with ischemic myocardiopathy in whom a heart transplant was indicated (LVEF < 35%), that PET detected myocardial viability in 50% of the patients for whom thallium-201 scintigraphy was negative. Thus, these patients underwent successful coronary bypasses with the same clinical outcome at 12 months as all the patients revascularized during the same year at the facility in question. This therefore made it possible to reserve heart transplants for the patients who actually required them, thus optimizing the allocation of this scarce resource. The study by Duong et al. [1995] showed, in 112 patients with ischemic cardiomyopathy (LVEF < 35%) who were being considered for a heart transplant, that 5-year survival in the patients with PET-evaluated myocardial viability who were vascularized was approximately the same as that in the transplanted patients (80% vs. 71%).

The recent study by Siebelink et al. [2001] involved 103 patients and is the only randomized, controlled study. Its objective was to compare prospectively two strategies, one PET-guided, the other SPECT-guided, for managing coronary patients who were being considered for myocardial revascularization. All the patients underwent FDG-PET and technetium-99m-sestamibi SPECT and were subsequently randomized to two groups in order to take the test into account in the management modality (bypass, angioplasty or pharmacologic treatment). After a follow-up of 28 ± 1 months, there was no statistically significant difference in terms of the occurrence of the main assessment criterion (cardiac event-free survival) between the two groups (11 events in the PET group vs. 13 in the SPECT group). The authors therefore conclude that either modality can be used equally for making revascularization decisions in patients suspected of having viable myocardium. It will be noted that only one third of the patients in this study had an LVEF of less than 30%.

A randomized, prospective, multicentre Canadian study, PARR Phase 2 [Beanlands, 2000-2001], is presently underway. It has a recruitment goal of 412 coronary patients with severe left ventricular dysfunction (LVEF < 35%). The study has a double objective. The main objective is to compare the clinical outcomes (composite criterion: cardiac deaths, cardiac arrests, infarctions, transplantation, admission to hospital for unstable angina, or heart failure) and the cost of PET-guided management with the outcomes obtained without PET (standard approach) at one and two years. The secondary objective is to compare left ventricular function and quality of life at one and two years of follow-up on the basis of the two management strategies. The results of this study should provide a better assessment of the clinical and economic impact of using PET in patients with severe left ventricular dysfunction, patients who benefit the most from revascularization techniques and in whom determining myocardial viability is essential for optimal management.

Presently, there are insufficient data to draw any conclusions, in light of the clinical assessment criteria, concerning efficacy and cost-effectiveness. Although it is of a high level of evidence, Siebelink et al.'s study [2001] is a low-power study of all manner of coronary patients. It would seem that it is not these patients who benefit the most from PET scanning, but rather more severely affected patients or patients with equivocal SPECT results. The PARR 2 study [Beanlands, 2000-2001] could provide answers to some of these questions and thus permit informed decision making.

4.3.5 The role of PET among the currently used nuclear medicine tests

In patients with minimal to moderate left ventricular dysfunction, the positive predictive value of stress echocardiography, digital SPECT and PET for identifying hibernating myocardium is comparable (69 to 83%), with a negative predictive value of between 81 and 90% [Winjs et al., 1998]. Dobutamine stress echocardiography is the least expensive and most widely available test. However, in patients with severe left ventricular dysfunction, the false-negative rate is greater than with nuclear imaging techniques.

PET is the method with the highest predictive value in patients with left ventricular dysfunction, according to Arrighi et al. [1997] and Fath-Ordoubadi et al. [1998].

The Alberta Heritage Foundation's assessment report [Cowley et al., 1999] on the different methods of evaluating myocardial viability indicates sensitivity and specificity ranges for the different diagnostic modalities discussed in the literature:

- PET: Sensitivity, 71 to 95%; specificity, 66 to 86%.
- Dobutamine stress echocardiography:
  - Low to moderate dose of dobutamine: Sensitivity, 60 to 97%; specificity, 30 to 94%.
  - High dose of dobutamine: Sensitivity, 60 to 87%; specificity, 83 to 90%.
- SPECT: Sensitivity, 72 to 100%; specificity, 38 to 98%.

The latest review, by Bax et al. (published in February 2001) [Bax et al., 2001], which involved a comparison of various noninvasive modalities for detecting hibernating myocardium (FDG-PET, thallium SPECT, dobutamine stress echocardiography), showed that FDG-PET had the highest sensitivity (93%, $p < 0.005$) and the highest negative predictive value (86%) in relation to the other techniques and that echocardiography had the lowest sensitivity (81%). However, stress echocardiography had the highest positive predictive value (77%, $p < 0.05$) compared to 71% for PET, and the best specificity (80% vs. 58% for PET).

These results should be interpreted with caution, since different study methodologies are found among the studies that were selected, in terms of both the heterogeneity of the participants, the assessment criteria, the protocols and the analytical methods. Furthermore, most of the studies involved patients with an LVEF > 35%.

One of the technical problems encountered with SPECT scanning is nonhomogeneous photon attenuation in the chest. Thus, attenuation artifacts reduce the specificity of image analysis, especially in obese patients and women with large breasts. The recent introduction of new multihead SPECT cameras might resolve these problems in the future.

In addition, new technologies or test methodologies are being developed and evaluated [Bengel et al., 1998]. Hybrid PET/SPECT cameras permit imaging with PET tracers, such as FDG, using new generations of scanners [Beller et al., 2000]. Also, magnetic resonance imaging has yielded promising preliminary results in this use [Kim et al., 2000].

4.3.6 Conclusion

From what is stated in the literature (arguments in favour of clinical benefit based on several studies with a low level of evidence and a single study of good methodological quality but of low power that did not involve patients who, it was thought beforehand, would benefit the most from PET), one cannot draw any firm conclusions as to the systematic introduction of PET in day-to-day clinical practice.

Nonetheless, PET permits an unprecedented evaluation, both quantitative and qualitative, of cardiac pathophysiological processes. It is a promising technology that is leading to numerous areas of research that will provide a better knowledge of cardiac processes, which may have important clinical applications in patient management.

The use of PET might make it possible to optimize the management and prognosis of more severely affected coronary patients through better selection of those in whom a heart transplant is truly indicated (certainty that there is no viable myocardial tissue) and through the use of revascularization only in those cases where myocardial viability has been demonstrated. Certain publications and our simulation concerning the clinical use of PET to assess myocardial viability suggest a favourable cost-effectiveness ratio.

In the field of cardiology, the clinical utility of PET is

recognized for the following uses:

- studying myocardial perfusion for the purpose of diagnosing and managing coronary artery disease; and
- studying myocardial viability;

and has potential for

- monitoring heart transplant patients (detecting posttransplant arteriopathy and measuring coronary reserve); and

- monitoring the effect of treatments and the response to therapy in coronary artery disease.

4.4 ECONOMIC CONSIDERATIONS

4.4.1 Australian assessment (MSAC)

The observations of the MSAC (Australia) will be used here as the latest guidelines for assessing the cost-effectiveness of PET [MSAC: Ghersi et al., 2000]. A few other references will be included and commented on.

The MSAC notes that models have mainly concerned non-small-cell lung cancer and solitary pulmonary nodules and that there is little information on the evolution of patients following PET scanning. Given that there are no direct measurements of PET's impact on quality of life and survival, the economic evaluations are based on intermediate evaluation measures of patients' clinical evolution. Only Gambhir et al. [1996] and Scott et al. [1998] have attempted to evaluate survival based on the reduction in the mortality associated with surgical procedures.

Nevertheless, the data tend to suggest that PET could generate savings [Gambhir et al., 1996; Valk et al., 1996; von Schulthess et al., 1998] or at least be cost-effective [Scott et al., 1998], if the upper limit of cost-effectiveness is set at $50,000 per life-year saved.

However, the MSAC notes that all the studies of the diagnosis and management of non-small-cell lung cancer used a simulation methodology and were therefore based on assumptions. It concludes that it would be advisable to validate, with clinical trials, the assumptions in those models, which are nonetheless plausible. Such trials are presently underway and will confirm or invalidate the results of the models.

From a narrower perspective, given the diversity of the data and of the methodologies used in these studies, it is difficult to make direct comparisons and to extrapolate the results to the situation in Québec. Furthermore, none of these studies explicitly factored in the cost of implementing PET in its methods of calculation. Lastly, it is possible that the models used do not represent a clinical and epidemiological approach specific to the situation in Québec.

4.4.2 1999-2000 update - Economic aspects

4.4.2.1 Literature review - Lung cancer

The economic studies of PET published after the MSAC report are summarized in Table 3.

Table 3: Literature review on the cost-effectiveness of PET in lung cancer

Year	Author, country	Citation	Use	Design	Results
2000a	Dietlein et al., Germany	Eur J Nucl Med 2000; 27:1441-56.	Management of patients with solitary pulmonary nodules	• Gambhir et al.'s model [1998] with modifications • Decision tree • Four strategies compared: wait and watch, exploratory surgery, transthoracic needle biopsy	Incremental cost-effectiveness ratio in relation to the wait-and-watch strategy: • 3,218 euros* • 4,210 euros per life-year saved for surgery • 6,210 euros per

				and PET	life-year saved for biopsy
2000b	Dietlein et al., Germany	Eur J Nucl Med 2000; 27:1591-7.	Management of patients with non-small-cell cancer	• Decision tree • Five strategies compared	Incremental cost-effectiveness ratio in relation to the conventional strategy. • 143 euros per life-year saved for PET

* 1 euro = 0.7403 Canadian dollars

■ Studies concerning solitary pulmonary nodules (SPNs)

The objectives of Dietlein et al.'s cost-effectiveness study [2000a] were to determine the impact of PET utilization on life expectancy and to estimate the incremental cost-effectiveness ratio for implementing PET.

A decision tree was constructed to assess the costs and efficacy, in terms of the number of life-years saved, of the four competing strategies for managing patients with SPNs: 1) wait and watch; 2) exploratory surgery; 3) transthoracic needle biopsy; and 4) PET. The parameters used in the model came from the literature. Only the following direct costs, which relate to the public insurer's perspective, were considered by the authors: hospitalization, PET, computed tomography, biopsy, surgery, mediastinoscopy and palliative treatment. Indirect costs were not considered. An annual discount rate of 5% was used, although the time horizon was not explicitly indicated.

The study population was a hypothetical cohort of 62-year-old operable men with SPNs of up to 3 cm, with no calcification, spiculae, metastases or recent history of extrapulmonary tumor diagnosed by computed tomography or chest x-rays.

A univariate sensitivity analysis was performed for the following variables in order to test the robustness of the conclusions: prevalence of solitary pulmonary nodules, specificity and sensitivity of PET and biopsy, surgical mortality rate, and costs of PET and palliative treatment.

In the baseline scenario, and in comparison with the wait-and-watch strategy, the incremental cost-effectiveness ratios of PET, biopsy and surgery are, respectively, 3,218, 6,120 and 4,210 euros per life-year gained. The results are different if the surgery strategy is substituted for the wait-and-watch strategy as the comparator. Thus, PET has a negative incremental ratio of 6,912 euros per life-year gained compared to 4,210 euros per life-year gained for the wait-and-watch strategy and 3,343 euros per life-year gained for the transthoracic needle biopsy strategy.

According to the authors, the results suggest that PET is cost-effective both for patients who are at risk and those not at risk for dying upon surgery. They conclude that, in applying American prevalence data, the budget impact of implementing and disseminating PET in a public program would be less than one euro per insured person.

■ Studies concerning non-small-cell lung cancer

The objectives of Dietlein et al.'s economic study [2000b] were to identify the groups of patients with non-small-cell cancer most likely to benefit from PET, to determine the potential savings that would result from introducing PET and to determine the role of PET in relation to mediastinoscopy in the arsenal for evaluating this disease.

A decision tree was constructed to assess the costs and efficacy, in terms of life-years gained, of five competing strategies: 1) computed tomography; 2) PET for patients with normal-size lymph nodes; 3) PET for all patients; 4) PET for all patients without mediastinoscopy if the computed tomography and PET scans are positive; and 5) PET for all patients without mediastinoscopy if the PET scan is positive. The parameters used in the model came from the literature. Only the following direct costs, which relate to the public insurer's perspective, were considered: hospitalization, PET, computed tomography, biopsy, surgery, mediastinoscopy and palliative treatment. Indirect costs were not considered. An annual discount rate of 5% was used.

The study population was a hypothetical cohort of 62-year-old operable men in whom the diagnosis of a tumor was made by computed tomography and bronchoscopy and confirmed histologically.

A univariate sensitivity analysis was performed for the following variables in order to test the robustness of the conclusions: the prevalence of mediastinal metastases, the specificity and sensitivity of PET, the sensitivity of mediastinoscopy, and the costs of PET and palliative treatment.

In the baseline scenario, and in comparison to the computed tomography strategy, the incremental cost-effectiveness ratios for the following strategies, 1) PET for patients with normal-size lymph nodes; 2) PET for all patients; 3) PET for all patients without mediastinoscopy if the CT and PET scans are positive; and 4) PET for all patients without mediastinoscopy if the PET scan is positive, are 143, 11,100, 24 and 19,830 euros, respectively, per life-year gained. The results are different if the PET strategy is substituted for the computed tomography strategy in patients with normal-size lymph nodes as the comparator. Thus, the incremental ratios for the following strategies, 1) PET for all patients; 2) PET for all patients without mediastinoscopy if the CT and PET scans are positive; and 3) PET for all patients without mediastinoscopy if the PET findings are positive, are, respectively, 36,667, 15,325 and 15,716 euros per life-year gained.

The results suggest that the scenario in which PET is used for all patients with normal-size lymph nodes would be more cost-effective than the competing options. The budget impact is acceptable in this scenario.

4.4.2.2 Studies of other uses in oncology and neurology

We did not find any studies evaluating the efficiency of PET in other oncological and neurological applications.

4.4.3 Study specific to Québec: non-small-cell lung cancer (NSCLC)

It is difficult to extrapolate the results of the two studies by Dietlein et al. [2000a; 2000b] to the situation in Québec. These authors attempted to identify the most efficient strategy for managing solitary pulmonary nodules (SPNs) and detecting metastases, using clinical algorithms reflecting the common practices in their health-care system.

In Québec, it is unlikely that this technology will be used by clinicians as a diagnostic tool for solitary pulmonary nodules because access will remain limited (even if this technology becomes available in Québec's health-care system).

Furthermore, given that the prevalence of lung cancer in patients with SPNs varies from 80 to 90% when they are referred to a tertiary centre, the use of PET will obviously be limited primarily to determining the degree of metastasis in order to assess the appropriateness of undertaking surgical treatment.

It was in considering these specific aspects that an analysis using Québec parameters was performed in order to be able to assess the economic impact and potential efficiency of PET in its implementation context.

4.4.3.1 Materials and method

An analytical model was developed to predict the cost and effects of using PET to detect mediastinal and distant metastases. To be able to compare the results with those of previous studies, the reference case technique recommended by the Washington panel was used in this analysis [Russell et al., 1996].

The costs and life expectancy were determined for each strategy examined. The explicit probabilities used in this model are presented in Table 4. Bayes' theorem was used to extract most of the probabilities. A health-care system perspective was adopted in this study. Only the direct costs were considered.

4.4.3.2 Construction of the decision tree

The prediction model (Figure 4, Appendix 11) was developed from several assumptions: the study population consists of a hypothetical cohort of 100 65-year-old males with histologically confirmed non-small-cell lung cancer in whom the preoperative metastatic evaluation, based on conventional detection techniques, is negative for mediastinal and distant metastases. The model thus excludes any patient with a positive preoperative evaluation. In addition, because of the number and types of scanners available on the market and of the lack of data on their efficacy, we assumed, for the sake of simplicity, that a dedicated, full-ring, multidetector PET scanner would be the type deployed in Québec.

The costs associated with the treatment required for the disease, such as chemotherapy and radiation therapy, were not included in our analysis. We assumed that a patient in whom surgical intervention is going to be avoided thanks to PET incurs the same chemotherapy and radiation therapy costs as a patient who is operated on and who had, prior to surgery, metastases that were not detected by conventional diagnostic methods. The model thus assesses the costs associated with the diagnostic tests, the surgery and the reimbursement for the medical procedures performed by health professionals. Consequently, the model mainly examines the difference in surgical costs between the two options.

4.4.3.3 Strategies

In the CT option, patients with positive results for mediastinal metastases undergo mediastinoscopy for the purpose of determining whether or not they are candidates for surgery. In those cases, where the CT findings are negative, the patient undergoes surgery.

As for the CT + PET option, all the patients are first evaluated by computed tomography. The use of PET is limited to detecting distant metastases when the CT scan is positive for mediastinal metastases and to detecting mediastinal metastases when the CT scan is negative. In the latter case, PET is also used for detecting distant metastases. To confirm the PET findings, biopsy and mediastinoscopy are used to detect the presence of distant metastases and mediastinal metastases, respectively.

4.4.3.4 Literature review: Data acquisition

The prevalence of mediastinal and contralateral metastases in patients with NSCLC has been estimated at 31% (range: 28 to 38%) in the literature [Gross et al., 1988; McLoud et al., 1992; Dillemans et al., 1994; White et al., 1994; Primack et al., 1994]. However, this figure is not the prevalence of NSCLC but rather that of N2 or N3 lymph node metastases in patients with a histological diagnosis of NSCLC who are eligible for surgery. As for the probability of distant metastases detected by PET and not detected by conventional methods, it varies from 5 to 11% [Valk et al., 1995; Bury et al., 1998; Gupta et al., 1999; Pieterman et al., 2000]. The baseline values and intervals to be used in the sensitivity analyses and the other variables used in this analysis are presented in Table 4.

Table 4: List of the variables used in the lung cancer model

Variable	Baseline value	Lower limit	Upper limit	Reference(s)
Fee* for biopsy (physician)	75			Medical Specialists' Manual, RAMQ
Fee for computed tomography (physician)	60			Medical Specialists' Manual, RAMQ, code 8262
Fee for mediastinoscopy (physician)	280			Medical Specialists' Manual, RAMQ, code 3036
Fee for PET (physician)	250			Medical Specialists' Manual, RAMQ, code 8700
Fee for surgery (physician)	672			Medical Specialists' Manual, RAMQ, code 3196
Cost* of hospital stay for mediastinoscopy	5,054	4,977	7,932	APR-DRG 076 (subgroup, code 46.81)
Cost of hospital stay for surgery	8,424	7,544	11,781	APR-DRG 075 (no subgroup, code 46.81)
Cost of hospital stay for biopsy	6,130			APR-DRG 076 (subgroup, code 89.00 and 90.90)
Cost of hospital stay for mediastinoscopy, biopsy and surgery	9,163	7,609	12,147	APR-DRG 075 (with subgroups 46.81, 89.00 and 90.90)
Cost of PET scan, including capital cost (hospital)	1,313			Appendix 10
Sensitivity of computed tomography	0.75	0.6	0.9	Pieterman et al., 2000
Specificity of computed tomography	0.66	0.55	0.77	Pieterman et al., 2000
Life expectancy** with palliative treatment	1	0.1	2	Scott et al., 1998; Gambhir et al., 1996
Life expectancy with surgical treatment	7	1	15	Cummings et al., 1986; Beck et al., 1982
Mortality rate associated with computed tomography	0.000025	0	1	Hartman et al., 1982
Surgical mortality rate	0.03	0	0.2	Williams et al., 1981; Evans, 1973; Ginsberg et al., 1983
Sensitivity of PET in detecting distant metastases	0.82	0.64	1	Pieterman et al., 2000
Specificity of PET in detecting distant metastases	0.93	0.88	0.98	Pieterman et al., 2000
Sensitivity of PET in detecting mediastinal metastases	0.91	0.81	1	Pieterman et al., 2000
Specificity of PET in detecting mediastinal metastases	0.86	0.78	0.94	Pieterman et al., 2000
Probability of metastases detected by PET	0.07	0.05	0.11	Valk et al., 1995; Bury et al., 1998; Gupta et al., 1999, Pieterman et al., 2000
Prevalence of mediastinal metastases	0.31	0.28	0.38	Gross et al., 1998; McLoud et al., 1992; Dillemans et al., 1994; White et al., 1994; Primack et al., 1994

* in Canadian dollars

** in years

Appendix 8 of this report (selected studies) was consulted for CT and PET sensitivity and specificity data. As regards the detection of mediastinal metastases, the sensitivity of PET is estimated at between 72 and 96%, with 90 to 100% specificity. As for its sensitivity and specificity in detecting distant metastases, Pieterman et al. [2000] estimate them at 82%

(range: 64 to 100%) and 93% (range: 88 to 98%), respectively. For analytical purposes, Pieterman et al.'s study was used as the main source of data for PET and CT sensitivity and specificity values, since it is the only prospective study that estimates the performance of PET and computed tomography in detecting mediastinal and distant metastases. Lastly, we assumed that the accuracy of biopsy as a diagnostic tool is 100%.

The mortality rate associated with the surgical resection of lung cancer reported in the literature varies from 2.4% [Williams, 1981] and 20% [Evans, 1973]. Ginsberg et al. [1983] report an overall mortality rate of 3.7% and a thoracotomy-specific mortality rate of 2.9%. We chose 3% (range: 0 to 20 %) as the baseline value in our analysis.

The risk of mortality associated with computed tomography is mainly due to the contrast agents used. A risk of 1 in 40,000 (0.0025%) is reported in the literature [Hartman et al., 1982]. The risk associated with FDG-PET is assumed to be negligible, since, to date, no complications or adverse effects have been reported in the literature.

Life expectancy was calculated according to the DEALE method, which was developed by Beck et al. [1982], where mean life expectancy = 1/(ASR + DSR). The ASR is the age-, sex- and race-adjusted annual mortality rate in the general population. DSR is the disease-related survival rate. In Québec, the life expectancy of a 65-year-old man is 15.64 years [Institut de la statistique du Québec, 2001]. The ASR is thus 0.067 (1/15.64). The DSR for a 2.3-cm lung tumor is 0.075 [Cummings et al., 1986]. The combined mortality rate for a typical patient is 0.142. His life expectancy (the reciprocal function of this sum) is 7 years. This figure was used in the baseline analysis, with a range of 1 to 15 years for the sensitivity analysis.

The life expectancy for inoperable cancers in patients with an advanced stage of the disease, based on radiographic findings, is estimated at 0.47 years [Gambhir et al., 1996; Scott et al., 1998]. Although there are certainly a few survival data for patients with mediastinal metastases that are not detected radiographically, these patients probably exhibit better survival than those in whom the chest x-ray is unequivocal. To take this into account, we assumed a life expectancy of 1 year (range: 0.1 to 2 years) as the baseline value for inoperable patients. As for the life expectancy of patients whose distant metastases are not detected by PET and for patients whose mediastinal metastases are not detected by computed tomography, it was estimated at 1 year.

The cost of a PET scan was estimated from the data presented in Appendix 10 of this report. We calculated that a PET scan costs $581, excluding the capital cost. The cost of a PET scan is $1,313, which includes the capital cost, or $732 more per scan. This figure was estimated on the basis of the following assumptions. We assumed a cost of $3.2 million for a scanner and of $4.3 million for a cyclotron. As for construction costs, we assumed that they were $500,000 for the cyclotron and $175,000 for the scanner. The life span of the scanner and that of the cyclotron were set at 10 and 25 years, respectively. Lastly, we used a 5% interest rate to take into account the loss of return on the capital, had it been invested.

The cost of the hospital stay for surgery alone, mediastinoscopy alone, biopsy alone and for all four interventions was determined by consulting the Ministère de la Santé et des Services sociaux's 1998-1999 APR-DRG database. The cost is $8,424, $5,054, $6,130 and $9,163, respectively. These average figures include the hospital stay and all the interventions and management that the hospital is to provide for the patient during the stay. Only the physicians' professional fees are excluded. For example, the costs associated with a CT scan are included in one of the APR-DRGs, excluding the physicians' fees.

The figures for the physicians' fees are from the Medical Specialists' Manual (September 1999 edition), published by the Régie de l'assurance-maladie du Québec, and are provided in Table 4 for each intervention. Lastly, the cost of a biopsy depends on the type. It can vary considerably. We therefore assumed an average cost of $75.

4.4.3.5 Analysis

The cost and life expectancy estimates for each option were obtained by adding the products of the probabilities and cost and life expectancy values. The mean cost-effectiveness ratios were used to evaluate the CT scan strategy in relation to the CT + PET strategy. The lowest ratio is that of the most efficient strategy. The incremental cost-effectiveness ratio (cost of the CT option - cost of the PET option)/(CT life expectancy - PET life expectancy) was used for the marginal analysis of PET efficiency.

Given the low accuracy of certain variables, a univariate sensitivity analysis was performed. This type of analysis consists in varying the values of a given variable in a predefined range while maintaining the values of the other variables constant, and assumes independence between the variables.

To take into account the interdependence between the variables, a Monte Carlo dynamic sensitivity analysis was performed in order to obtain a 95% confidence interval for the costs, efficacy and cost-effectiveness ratio. This type of simulation executes the model numerous times (1,000 in our analysis), modifying the values of all the variables simultaneously, using a predefined probability distribution. This approach provides a distribution of samples and therefore descriptive values (mean, median, maximum, minimum and probability distribution) for the result. The variables, their ranges and their predefined distributions are shown in Table 48 (Appendix 11).

Given that the time horizon for the analysis was one year, no discounting of the costs or effects was necessary.

Table 5: Results for each strategy per patient (lung cancer)

Strategy	Cost	Incremental Cost	Efficacy (life-years)	Incremental efficacy	Mean cost-effectiveness ratio	Incremental cost-effectiveness ratio
CT	$8,455		4,551		$1,858 per life-year	
CT + PET	$9,723	$1,268	4,823	0.27	$2,017 per life-year	$4,689 per additional life-year gained

4.4.3.6 Results

Table 5 shows the results per patient and the costs, efficacy, mean cost-effectiveness ratios and the incremental cost-effectiveness ratio.

In general, the mean cost-effectiveness ratios suggest that PET is almost as efficient an intervention as computed tomography, the mean cost-effectiveness ratio for PET being slightly higher than that for computed tomography. The mean cost of the CT strategy is $8,455 per patient compared to $9,723 for the PET strategy, for a cost differential of $1,268. The PET strategy extends life expectancy by slightly more than three months (0.27 years) compared to survival with the CT strategy.

As for the incremental cost-effectiveness ratio, i.e., the cost associated with one additional life-year gained, it is $4,689. Considering the number of new cases and the prevalence of mediastinal metastases, 1,837 new patients a year could potentially benefit from this technology. The budget impact, from the perspective of the incremental cost, i.e., the additional cost to the health-care system, would be $8,613,693. If we perform the same analysis but exclude the capital cost from the cost of PET scanning, the incremental cost-effectiveness ratio would be $1,983, with a budget impact of $3,642,771.

Table 49 (Appendix 11) shows the results of the univariate sensitivity analysis for all the variables included in the model. It can be seen from the results that the variation in the baseline values of the variables does not have an impact on the decision, the mean cost-effectiveness ratio for the PET strategy always being higher than that for the competing option.

Figure 6 (Appendix 11) is a graph of the Monte Carlo simulation for the incremental cost-effectiveness ratio. It can be seen that most of the simulations are in the right quadrant, the quadrant where PET improved life expectancy while at the same time requiring an investment for each additional health gain. Table 50 (Appendix 11) shows the mean, median and quartiles for the incremental cost, efficacy and cost-effectiveness ratio values, as they appear in the dynamic sensitivity analysis.

Table 51 (Appendix 11) shows the frequencies of occurrence of incremental cost-effectiveness ratios, by intervals, of the 1,000 Monte Carlo simulations. It can be seen that in 95% of the cases, the incremental ratio is less than $50,000 per life-year gained.

4.4.3.7 Discussion and conclusions

Our study suggests that PET is a cost-effective intervention in the specific context of its clinical utilization and deployment in Québec. Thanks to the reference case technique, we were able to compare our results with those presented in the literature. We note that they are similar to the results compiled by the MSAC, that is, that PET can lead to savings or require only a very small and very acceptable investment for each life-year gained, provided the purchase cost, which is high, has been amortized.

Our univariate and Monte Carlo sensitivity analyses confirmed the robustness of the results. Table 49 (Appendix 11) shows that varying the baseline values does not significantly affect the results, the incremental cost-effectiveness ratio ranging from $3,000 to $5,000 per life-year gained.

Table 51 (Appendix 11) shows the distribution of the incremental cost-effectiveness ratios. It can be seen that, in about 50% of the simulations, the investment required to gain one life-year is less than $5,000. In 73% of the cases, it is less than $10,000, which is not, in itself, a very large investment. If the standard cost-effectiveness ratio is set at less than $50,000 per life-year gained, 95% of the simulation cases would be below this figure. Thus, economically, PET would not necessarily generate any savings in the health-care system, but it might avoid unnecessary surgeries and therefore, to a certain extent, shorten the waiting lists and contribute to the overall efficiency of the health-care system.

Using the available data, we attempted to assess the economic impact and efficiency of PET on clinical outcomes and the health-care system. Since there is no direct measure of patient survival, we used an intermediate endpoint, such as the reduction in the mortality due to surgical procedures. However, using such an indicator does not enable us to fully assess the utility of PET. In the short term, it is unlikely that PET will improve survival in patients with lung cancer. The efficacy of PET resides instead in its ability to improve the patients' quality of life by sparing them an unnecessary, debilitating intervention and providing them with quicker access to treatment, on the one hand, and to enable them to express their preferences in terms of the clinical approach to be used, on the other. Quality-of-life and patient preference measurements obtained by prospective studies will permit a more adequate assessment of the efficacy of this technology.

We included the costs required to implement PET in Québec. For analytical purposes, we considered a very cautious scenario and assumed that this technology would be used only to detect local and distant metastases in patients with NSCLC. Given that this technology would be used for clinical purposes other than detecting metastases in patients with NSCLC, the capital cost should not be done on the basis of this single application. Thus, the capital cost to be included in the cost of PET scanning would probably be less than $732 per use, which would significantly reduce the incremental cost-effectiveness.

Because the analysis is limited to a single clinical use (the detection of metastases in cases of non-small-cell lung cancer) and to a very limited population, other studies are needed to confirm PET's efficiency or lack thereof in other applications. Our prediction model estimates the reduction in the number of surgeries at 12%, with patient survival prolonged by three months. These figures are similar to the results of a randomized, prospective study [van Tinteren et al., 2000] presented at the 2000 ASCO conference.

In conclusion, with the current state of knowledge and from an economic perspective specific to the situation in Québec, our model shows that the use of PET to detect local and distant metastases in NSCLC is potentially an intervention that would require an acceptable investment for each life-year gained.

4.4.4 Study of myocardial viability in the Québec context: An exploratory analysis of the potential impact

In the very near future in Québec, it is likely that PET will be used in cardiology mainly for detecting viable myocardium that can respond favourably to revascularization.

At this time, only a few efficacy studies are available for estimating the potential impact of PET as a diagnostic tool in this application. Furthermore, no economic evaluation of this clinical application is, to our knowledge, available. This lack of data makes it difficult to assess the anticipated efficacy of PET in this disease.

The literature abounds with differing opinions about the usefulness of models in this specific problem. Some authors do not see this approach as having any validity, while others maintain that early modelling is an important means of aiding the decision-making process. They recognize the need to use different analytical approaches to make up for the lack of experimental data. They also recognize that utilizing the results of an early model to determine research priorities does have its usefulness.

This is where our analysis comes in. Our objective was to model the use of PET to detect myocardial viability and to assess its potential impact. The results of this modelling will enable us to make a global assessment of PET's utility at this stage of its development. To this end, a Monte Carlo-type mathematical model was used for the analysis. This approach yields results in the form of intervals with a predefined level of confidence. The objective of this analysis is not to provide accurate data, but rather to estimate, in an exploratory manner, the anticipated economic impact of PET in this specific clinical application, i.e., evaluating myocardial viability.

4.4.4.1 Materials and method

Given the context in which PET will be used in Québec and the availability of data in the literature, we adopted, for the purposes of this analysis, a data extraction approach by surveying expert clinicians. Expert clinicians at Hôpital Laval in Québec City were consulted for the purpose of developing decision trees, determining the explicit probabilities for the variables and determining the population for which the technology would be used first. A list of the experts who were consulted is provided in Appendix 12.

The decision tree that was constructed is shown in Appendix 11 (Figure 8). For patients with severe left ventricular dysfunction who have not previously undergone coronary angiography, which is the case for about half of the patients in tertiary cardiology, when the clinician needs to make a diagnostic and therapeutic assessment, the use of PET on a first-recourse basis may be an attractive option.

In current clinical practice, where the use of PET is not possible, the clinician, in about one half of the cases, will first perform coronary angiography. If he or she detects coronary artery disease, he or she will, in 75% of these patients, then have to determine their myocardial viability. The use of conventional modalities, i.e., SPECT or stress echocardiography (dobutamine) will be inconclusive or "negative" in 50 to 75% of these cases, which will lead the clinician to make a relatively arbitrary decision regarding the possibility of revascularization (or to opt for transplantation or pharmacologic treatment).

For each strategy examined, the costs and the proportion of individuals surviving at five years were estimated. The explicit probabilities used in the prediction model are based on the variables presented in Table 6. A health-care system perspective was adopted in this study. Only the direct costs were considered. The costs associated with the use of medical services and the reimbursement of professional fees were estimated for each strategy.

The cost of a PET scan was estimated using the method described in Section 4.4.3.4. The cost of a thallium scan was estimated from financial report AS-471 and expert opinions. It is $350. This figure includes the cost of the procedure and that of the radiotracer. The cost of revascularization was obtained by consulting the 1998-1999 APR-DRG database. The costs of medical treatment and transplantation were obtained from expert opinions. They are $20,000 and $60,000, respectively. This latter figure does not include the cost of obtaining an organ or of the coordination involved in a heart transplant, given that the time horizon in our analysis precedes transplantation. The figures used for the physicians' fees are from the Medical Specialists' Manual (September 1999), publish by the RAMQ. For the purposes of our analysis, a variation of ± 20% was applied to each cost component in order to obtain an interval. These costs are shown in Table 6.

For measuring efficacy, we used the patients' mean probability of survival at five years after revascularization, medical treatment and/or transplantation.

Lastly, the study population consists of a hypothetical cohort of male patients with a left ventricular ejection fraction of less than 30%.

Table 6: List of the variables used in the myocardial viability model

Description	Value	Source
Cost* of a PET scan (hospital)	1,050 - 1,575	Appendix 10
Fee* for PET (physician)	225 - 275	Medical Specialists' Manual (RAMQ)
Fee for a thallium scan (physician)	94.4	Medical Specialists' Manual (RAMQ)
Cost of revascularization	8,262 - 10,099	APR-DRG
Cost of a thallium scan (hospital)	315 - 385	Financial report AS-471
Cost of medical treatment	16,000 - 24,000	Expert opinion
Cost of transplantation	48,000 - 72,000	Expert opinion
5-year postrevascularization survival probability	0.8	Expert opinion
5-year post-medical treatment survival probability	0.5	Expert opinion
5-year posttransplantation survival probability	0.75	Expert opinion
Probability of medical treatment	0.6 - 0.95	Expert opinion
Probability of an unequivocal thallium scan	0.3 - 0.4	Expert opinion
Probability of viable myocardium when the thallium scan is equivocal in the thallium-alone option	0.15 - 0.3	Expert opinion
Probability of viable myocardium when the thallium scan is equivocal in the thallium + PET option	0.5	Beanlands et al. 1997, Dreyfus et al. 1994

* in Canadian dollars

4.4.4.2 Analysis

The mean and incremental cost and efficacy intervals were used to compare the PET option with the no-PET option. These intervals were generated by a Monte Carlo analysis. This type of simulation executes the model numerous times (1,000 times in our analysis, with a 95% confidence level), modifying simultaneously the data and randomly choosing values from a predefined probability distribution. The variables and their predefined distribution are shown in Table 52 (Appendix 11).

4.4.4.3 Results

Table 7 shows the results and the 95% confidence intervals for the costs, the 5-year survival probability, the incremental cost and the incremental efficacy.

Table 7: Results of the economic analysis for myocardial viability

Strategy	Cost ($)	Efficacy	Incremental cost ($)	Incremental efficacy
Thallium + clinical decision	10,547 to 29,993	0.63 to 0.71		
Thallium + PET	10,119 to 24,753	0.69 to 0.73	-7,182 to 687	0.02 to 0.07

The thallium + PET strategy seems to be the most cost-effective option. It appears to be less expensive, and its efficacy is superior to that of the thallium-alone strategy. It seems that PET, based on the basic assumptions, would yield savings for the health-care system (the incremental cost is negative).

Figure 7 (Appendix 11) is a graph of the incremental cost-effectiveness ratio simulation results. Each point represents a simulation. It can be seen that almost 100% of the points are in the left quadrant, which means that the thallium + PET strategy would yield savings and at the same time be more effective, with a 95% confidence level.

As for efficiency, i.e., its cost-effectiveness, our model, which is based on several assumptions (efficacy, target population and costs), suggests that PET is a very cost-effective intervention.

4.4.4.4 Discussion and conclusions

Our objective was to estimate the efficiency of PET in detecting myocardial viability. Our preliminary analysis, based on a Monte Carlo-type dynamic simulation, suggests that PET is a very cost-effective intervention in the context of tertiary cardiology centres when used for a specific purpose in a population of patients with an ejection fraction of less than 30%.

However, this finding needs to be qualified. Since there are no available data in the literature, our sources of data were mainly expert opinions. Despite the inherent weakness of this approach, its use in certain types of economic studies should not be avoided. Data from randomized clinical studies and formal literature reviews certainly provide more-valid data, but when there is a paucity of data from such sources, one must resort to other methods, especially in a context of diffusing new technologies, such as PET in cardiology.

Given that the time horizon for the analysis in cardiology was several years, the costs and consequences should have been discounted. However, for the sake of simplicity, this was not done. It is unlikely that discounting would have reversed the result, that is, that PET is very cost-effective. To compensate for the uncertainty concerning the accuracy of the data, we used intervals rather than estimates and a Monte Carlo-type dynamic simulation. Using this strategy enabled us not to overestimate or underestimate the efficacy and cost data. As for the variables that were kept constant, the sensitivity analysis performed for these variables reveals that varying the baseline values does not affect the results.

Although this is early modelling, if we accept its limitations, it suggests that PET might be more efficient, because the analysis is limited to assumptions and to a very small population, and that further studies are necessary, especially in the case of using PET as a diagnostic tool for coronary artery disease and myocardial viability. Perfusion studies are performed to detect the presence of coronary artery disease, since in the vast majority of noncoronary cardiomyopathies, there should be little or no alteration of the regional myocardial flow or coronary reserve. Thus, PET could potentially lead to savings in coronary angiography utilization. In addition, in the case of coronary artery disease, a combined myocardial perfusion and myocardial viability PET study might enable one to determine if there is any benefit in revascularizing and, if the absence of viability is not demonstrated, to avoid performing coronary angiography and any other subsequent diagnostic test.

In conclusion, given the current state of knowledge and with an economic perspective specific to the situation in Québec, we note that the use of PET for detecting myocardial viability seems to be an efficient intervention. However, it would be important to document evidence of the incremental efficacy of PET in relation to the diagnostic tools that are currently available.

4.4.5 Studies concerning other uses in oncology and neurology

No study on the other uses of PET was carried out. The efficiency of PET in these clinical applications, specifically for Québec, is unknown.

4.5 GRADING CLINICAL USES

Referring to the conclusions stated above in this section for each of the uses and rearranging them, not by discipline and by use, but rather according to the recognition of the clinical use in each discipline, we obtain the following grouping:

- Clinical uses said to be recognized if the hard data are acceptable (in terms of clinical efficacy);
- Potential, if the hard data are acceptable but incomplete; and
- Not recognized, if the data are insufficient to reach a verdict, if they demonstrate nonperformance or if hard data were not found during the literature surveys performed for the purposes of this report.

It will be noted that this classification reflects the current hard data rather than a limited opinion about the use of this technology.

4.5.1 Recognized clinical uses

4.5.1.1 Oncology

- **Lung cancer**
  - Characterizing solitary pulmonary nodules.
  - Initial staging when a diagnosis of non-small-cell lung cancer is made, including:
    - detecting mediastinal lymph node metastases; and
    - detecting distant metastases.
- **Colorectal cancer**
  - The preoperative detection of hepatic and extrahepatic metastases in the context of detecting localized recurrence.
  - Determining the location of recurrence in the presence of clinical symptoms or abnormal paraclinical findings (conventional imaging, carcinoembryonic antigen, etc.).
  - Differentiating between residual tumor and postoperative scar when diagnostic imaging reveals abnormalities.
- **Melanoma**
  - Detecting extranodal metastases during the initial workup or the postoperative follow-up.
  - Evaluating a potentially treatable recurrence.
- **Head and neck cancer**
  - Identifying an unknown primary tumor in the presence of cervical lymph node metastases.
  - Staging cervical lymph nodes when conventional imaging is negative.
  - Detecting recurrence or residual tumors and differentiating between a tumor and postoperative scar.
- **Lymphoma**
  - Staging when restaging could influence the choice of treatment.
  - Evaluating residual disease after treatment.

4.5.1.2 Neurology and psychiatry

- **Refractory epilepsy**
  - Localizing epileptogenic foci in patients with refractory epilepsy who are candidates for surgery and in whom the information on the location of the foci (usual work-up, including seizure semiology, EEG and magnetic resonance imaging) is inconclusive.

- **Brain tumors (mainly glioma)**
    - Evaluating residual lesions after treating recurrent glioma and differentiating between radionecrosis and recurrence in patients treated with radiation therapy with abnormalities on diagnostic imaging.

4.5.1.3 Cardiology

- **Myocardial perfusion studies**
    - Diagnosis and management of coronary artery disease.
- **Myocardial viability studies**

4.5.2 Potential clinical uses

4.5.2.1 Oncology

- **Lung cancer**
    - Monitoring response to therapy.
    - Detecting recurrence or residual tumors.
- **Colorectal cancer**
    - Monitoring response to therapy.
- **Hodgkin's and non-Hodgkin's lymphoma**
    - Evaluating response to therapy during treatment.
- **Breast cancer**
    - Staging of primary and recurrent tumors.
    - Detecting axillary and internal mammary lymph node metastases.
    - Detecting the primary tumor in the context of an equivocal complete evaluation.
    - Monitoring response to therapy.

Mention is made in the literature of avenues of clinical utility in particular circumstances for the following cancers, which were not examined in this report: gynecologic cancers (ovarian, uterine, cervical), certain genitourinary cancers (testicular, metastases from hypernephromas), mesotheliomas, soft-tissue sarcomas, esophageal cancer, and pancreatic cancer.

4.5.2.1 Neurology

- **Brain tumors (mainly glioma)**
    - Initial staging of patients suspected of having a primary brain tumor, in order to guide the biopsy to the highest area of activity.
    - Evaluating the progression of a low-grade glioma to malignancy.
    - Preoperative workup.
    - Histologic grading of tumors.
    - The choice of treatment.
    - Determining the prognosis.
    - Detecting metastases.

4.5.2.2 Cardiology

- Monitoring heart transplant patients (detecting posttransplant arteriopathy and measuring coronary reserve).
- Monitoring the effect of treatments and response to therapy in coronary artery disease.

4.5.3 Unrecognized clinical uses

4.5.3.1 Oncology

- **Colorectal cancer**
    - Diagnosis of the primary lesion.
- **Melanoma**
    - Detecting lymph node metastases.
- **Head and neck cancer**
    - Monitoring response to therapy.
- **Prostate cancer**

4.5.3.2 Neurology and psychiatry

- **Alzheimer's disease**
    - The clinical utility of PET is not recognized, since there is presently no treatment, but it could play a role in the differential diagnosis of dementia and other cognitive diseases, such as Parkinson's disease.

It will be noted that this classification reflects the conclusions of recent assessment reports available in 2000 and available hard data gathered up to February 2001. As was seen, for example, with the clinical use of PET in lymphoma, it sometimes only takes a few weeks for new publications to corroborate the recognition of these uses or to move certain uses from the "potential" category to the "recognized" category.

It will also be noted that, although this classification will change quickly over the next few months because of clinical data, the efficiency data on PET still need to be strengthen, as indicated in the studies (discussed above) concerning the economic aspects of this technology.

5. DISCUSSION

5.1. ASSESSMENT OBJECTIVES AND STRATEGY

The objectives of *AÉTMIS's* assessment are:

1. To gather hard data on the clinical use of PET in different fields, in particular, oncology, neurology and cardiology; and
2. To make recommendations concerning the possible deployment of PET in Québec.

When these objectives were set out, PET's efficacy in a certain number of clinical applications was taken for granted. Once constructed, the list of these applications, together with economic estimates, would serve as a basis for recommendations concerning the deployment of this technology in Québec.

Ideally, the demonstration of the clinical efficacy of a given diagnostic test should be based on the following conventional criteria: 1) its performance in terms of sensitivity, specificity and the other usual parameters (positive and negative predictive values, etc.); 2) the uniqueness of the information obtained in relation to other tests; 3) the improvement in patient management in terms of beneficial outcomes; and 4) acceptable cost-effectiveness, given the perspective adopted.

In light of the data gathered thus far, the range of responses seems vast. For current and potential users, the clinical utility of PET has been demonstrated for a very large number of applications, and this technology should be deployed immediately in Canada and Québec.

For reimbursement organizations (e.g., the DHAC-DTB in Australia and the HCFA in the United States) faced with a technology that is already deployed in their countries, after several years if not decades of research, the conclusions concerning the recognition of PET's clinical efficacy are still guarded.

An evaluation of the existing data suggests that the demonstration of the efficacy of PET when used for clinical purposes is only partly supported. The DHAC-DTB recognizes several clinical applications, but they are being covered on a temporary basis until the existing data are completed with performance validations and economic studies. Furthermore, explicit conditions concerning the qualifications of clinical staff and the implementation of quality assurance protocols must be met in order to obtain reimbursement. Additionally, while the HCFA recognizes several reimbursable applications, coverage of these uses is subject to various conditions.

This difference between the current and potential users and the coverage policymakers shows the extent to which the modalities used by the different players concerned for evaluating PET's efficacy differ. For current and potential users, the demonstration of PET's efficacy is, in general, based on expert opinions based, in turn, on publications selected according to unstated criteria.

For organizations and task forces whose mandate has been to study coverage requests for PET scans (e.g., the VA-TAP, MSAC, DHAC-DTB, BCBSA and HCFA), the criteria for assessing the studies submitted in support of the requests are explicit, verifiable and supplemented with consultations with expert groups. These still-recent, various attempts by reimbursement organizations and assessment agencies to apply an appropriate evaluative process to PET reflect the difficulties inherent in assessing diagnostic tests or examinations [Fryback et al., 1991]. In this regard, mention will be made of the difficulties experienced by the Department of Veterans Affairs in 1996 and in 1998, despite efforts to establish appropriate assessment criteria [Adams et al., 1997].

AÉTMIS opted for a methodology equivalent to that in previous reports, modifying the assessment criteria as follows: in addition to selection criteria identical to those of the VA-TAP and MSAC, the methodological assessment criteria were the same as those used by these two organizations and were supplemented with the explicit requirement that a study compare PET with another technology in order to make it a higher-grade study (see Table 19 in Appendix 6).

It will be recalled that the strategy chosen by *AÉTMIS* consisted in accepting the conclusions of reports based on a structured assessment methodology, then in carrying out an update on the publications that postdate these reports, from 1999 to February 2001. In these circumstances, the quality of the studies cited in the previous reports was not reassessed. Occasionally, articles prior to 1999 were consulted or evaluated if they had not been included in the previous reports. This approach was identical for each of the areas of application examined, i.e., oncology, neurology and cardiology.

While the assessment of the methodological quality of studies is the same for the different areas of application, the measurement of the ultimate effects of PET scanning may differ according to the type of patients. Two examples in oncology and one in cardiology will illustrate these differences. Because of the poor survival prognosis in non-small-cell lung cancer, the clinical efficacy of PET may reside in the avoidance of unnecessary surgical interventions, which would lead to an increase in survival by reducing the complications of these interventions. The judicious use of PET in lymphoma could translate into increased survival, although there is still insufficient data in this regard. In cardiology, a change of clinical decision can have an immediate and measurable impact on patient health. Here, too, hard data are still not available, although some studies in progress might provide information in the near future.

The economic models constructed by *AÉTMIS* were aimed at compensating for this lack of data.

5.2 ECONOMIC CONSIDERATIONS

The observations of the MSAC (Australia) were used, to a large extent, as the latest guidelines for assessing the cost-effectiveness of PET. Although, according to the MSAC, the hard data are still not sufficient to draw any firm conclusions as to the efficacy and cost-effectiveness of PET, recent data and our models tend to suggest that PET may be cost-effective for the two cases in question, i.e., the staging of non-small-cell lung cancer and detecting myocardial viability. The models even suggest that, for these applications, PET could generate savings or at least be cost-effective if the upper limit of cost-effectiveness acceptability is set at $50,000 per life-year saved.

However, all of the studies use a simulation methodology. They are thus based only on assumptions, not on validated data. In addition, the MSAC concludes that it would be advisable to validate, with clinical trials, the assumptions in these models, which are nonetheless plausible. Such trials are presently underway and may enable one to confirm or invalidate the results of these models.

From a narrower perspective, given the diversity of the data and methodologies in these studies, it is difficult to make direct comparisons and to extrapolate the results to the situation in Québec, for the models used may not represent a clinical, epidemiological and economic approach specific to the situation in this province.

Assuming limited diffusion of PET at the outset and in light of the epidemiological and economic data specific to the situation in Québec, two models were constructed, one for non-small-cell lung cancer (Section 4.4.3), the other for myocardial viability (Section 4.4.4). The results of these studies suggest that PET is a cost-effective intervention for staging non-small-cell lung cancer. As for detecting myocardial viability, based on the available preliminary data and given the very nature of the potential impact of PET on patient management, PET is potentially very cost-effective.

As regards uses other than those mentioned above, PET's efficiency remains an unknown in the Québec context, as in most other health-care systems.

To illustrate the rapid pace at which economic data are changing, mention will be made of an article published after our survey cut-off date. It concerns a model applied to the use of PET in colorectal cancer (Park et al., 2001) and indicates that adding PET to computed tomography is cost-effective for staging.

5.3 LIMITATIONS OF THE ASSESSMENT

As in a good number of industrialized countries, although the situation has still not been generalized on a worldwide scale (see Appendix 3 for the geographic distribution of PET), Québec's health-care system is witnessing a fait accompli: a particular research technology has gradually developed over the past 25 years or so. During the last decade, manufacturers have focused on its use for clinical purposes, placing increasingly sophisticated equipment on the market. For about the past five years, health-care systems have been facing strongly mounting pressure to cover PET scans, yet there is no real evidence of this technology's efficiency.

This situation is a close repeat of the assessment of computed tomography. Over 20 years ago, the first formal assessment of this technology encountered the methodological difficulties evaluating diagnostic tests and the absence of cost-effectiveness data. It will be noted, however, that this aspect was barely beginning to be taken into consideration by health-care system policymakers [Banta and McNeil, 1978].

This situation is also similar to that of the assessment of magnetic resonance imaging (MRI) some ten years later, where the efficacy and efficiency evidence was also scarce when this technology was first used for clinical purposes. The parallel between MRI and PET was noted by the VA-TAP's evaluators [Adams, 1997]. They cite the first exhaustive study of the clinical efficacy of MRI [Cooper et al., 1988] and the research leading to the observation that the more explicit the assessment criteria, the less favourable the conclusions regarding the clinical use of MRI [Kent and Larsen, 1988].

To compensate for the lack of hard data and not delay the development of this new yet promising technology, it was, at the time, suggested [Chalmers, 1988] that patients be enrolled in approved studies as a means for a third-party payer to subsidize the first studies. This would reduce the risk of paying for tests the demonstration of whose efficacy was still only in the preliminary stage. This suggestion has been echoed in the case of PET.

It would still be an appropriate suggestion, since, with new promising technologies, there is once again the question as to whether a still-preliminary demonstration of the clinical efficacy of a given technology, as is the case with PET, is enough to justify coverage by a public body without it first requiring efficiency data on the new technology.

The coverage conditions imposed in Australia and even in the United States seem, to a large extent, to be aimed at checking the first-recourse use of PET and in making up for the lack of data on a large number of patients by compiling such data as reimbursements are made. The idea, it seems, is a bit as if administrative data could, at the end of the day, be used in place of data acquired from comparative studies.

In other words, by imposing restrictions on the use of PET, these health-care systems seem to be approving the awarding of grants on a one-by-one basis, since there are no complete dossiers on the clinical efficacy of this new technology to rely on. Furthermore, Australia's DHAC-DTB (a ministerial body), which endorsed the recommendations made by the MSAC (assessment organization) expects data to be gathered that will document the efficiency of the different uses of PET, in addition to formal research that is currently underway in this area. The Australian and American approaches could help guide the clinical use of PET until the anticipated additional hard data become available.

However, the means by which these additional data are acquired will pose numerous challenges both to the users, evaluators and policymakers, for technological improvements are occurring at such a rapid pace that studies set up for the purpose of generating the hard data that are lacking at the present time could be outdated before they are completed.

A similar comment could just as well be made about the technologies that "compete" with PET, such as computed tomography and magnetic resonance imaging or other nuclear medicine modalities that continue to advance. Indeed, it is expected that technological advances will lead to hybrid technologies combining an increased capacity of computed tomography for anatomical localization with an increasingly refined measurement of the metabolic activity in the observed lesions. The objectives of this report did not include this aspect of the evolution of related technologies.

From a broader perspective, it should also be mentioned that government agencies do not perform formal, rigorous clinical and economic assessments of most of the commonly used diagnostic tests. This still-recent assessment process has become more rigorous over the past few years, and this change has created, in potential users, the impression that a "new standard" for assessing diagnostic tests has been established for PET.

This advance in the assessment and acceptance criteria for a new technology illustrates, with the example of PET, the now-generalized need to tightly manage limited resources.

6. SUGGESTIONS FOR DEPLOYING PET IN QUÉBEC

6.1 CLINICAL NEEDS

In all the areas of PET utilization, the list of applications whose efficacy is recognized is getting longer by the day. As a result, the clinical uses enumerated in Chapter 4 do not constitute a closed list. The enumeration of recognized and potential uses raises the issue of the number of patients who could benefit from this technology.

However, for now, the number is very hypothetical, mainly because of the diversity of the applications. A compilation of the incidence rates of the diseases for each recognized application would help approximate the extent of the needs. Incidence can, of course, serve as a starting point, and the general epidemiological data found in Chapter 4 would enable us to do this. However, the number of patients who could benefit would have to be estimated, using management algorithms appropriate for each type of disease (complementarity with existing tests and examinations, clinical decisions, etc.). Such information from algorithms was not compiled within the framework of this report.

Furthermore, a number of adjustments would have to be made to prevalence data, since, in oncology, for example, any patient in remission is considered a prevalent case, which would probably distort the hypothetical PET utilization rates upwards, unless corrections are made to take into account the prognosis, the length of time before recurrence, survival times, etc. Thus, the incidence or prevalence data will have to be weighted on the basis of the recognized roles of PET for the different specialties.

Models of these estimates were not performed within the framework of this assessment. However, based on the opinions expressed by the members of the advisory committee, the number of patients in Québec who could benefit from PET would put the annual number of scans at about 15,000 or more.

The applications of PET with a potential for clinical use are an immediately fertile ground for validating the efficacy and efficiency of these uses, and the validation activities would be highly relevant to the new-technology assessment mandate that university hospital centres and university institutes have under An Act respecting health services and social services (R.S.Q., c. S-4.2, ss. 88 and 89, amendments of June 15, 2000), provided they are equipped with PET.

In brief, however approximately they have been determined, there seems to be sufficient clinical need to justify the appropriate deployment of PET at facilities that serve oncology, cardiology and neurology patients. For some of these facilities, it would be advisable to link the clinical activities with the assessment and research activities in order to promote the acquisition of the data needed for optimal PET utilization in Québec.

6.2 PHYSICAL AND HUMAN RESOURCES REQUIRED FOR PET

The cost of providing space and purchasing a sufficient number of cyclotrons and scanners for Québec can be briefly estimated. Based on the figures presented above, about 15,000 scans per year, at the rate of about 1,500 per scanner per year, calculated on the basis of one 8-hour shift per day, would monopolize at least about 10 scanners. This approximate calculation does not, however, take into account the operational aspects specific to each area of application. For example, in oncology, a PET scan may be performed daily on a larger number of patients than perfusion scans in cardiology with ammonia. We could thus consider adding, for the purposes of our calculations, a few more scanners to take this situation into account.

While the number of scans per scanner depends on the type of application, the short half-life (a few minutes or less) of certain isotopes makes transporting them over long distances unfeasible and requires a cyclotron near the patient, especially for perfusion studies in cardiology. In these conditions, the number of cyclotrons could be increased according to the number of sites chosen, for perfusion can be measured by means of rubidium-82 as rubidium chloride, oxygen-15 as water or nitrogen-13 as ammonia. No rubidium generator has been approved by Health Canada. Oxygen-15 is used mainly in research.

Thus, the production of ^{13}N for clinical purposes will require a cyclotron near facilities that perform heart scans. See Chapter 2 and Appendices 1 and 2 for further details on half-lives and transport.

Myocardial perfusion can be measured with SPECT using radioisotopes that have longer half-lives than that of ^{13}N, e.g., thallium-201 and technicium-99m, and myocardial viability can be evaluated with ^{18}FDG. In such cases, there is no need to have a cyclotron near the facility.

Since a cyclotron can provide the necessary radioisotopes for operating about three or four scanners, it would take about three or four cyclotrons to supply 10 or 12 scanners.

Since there are already two cyclotrons in Québec, namely, in Sherbrooke and Montréal, adding a third and a fourth or even a fifth cyclotron, which would be located at an appropriate distance from the new PET centres, could, together with the two existing cyclotrons, meet the need for radioisotopes for all of Québec.

Without repeating the cost figures used in the models in Section 4.4 or all the ranges for the costs of the different components (providing space for scanners and cyclotrons, purchase of equipment, supplies and service contracts inherent in PET operations; see Appendix 10), it can be said that the overall cost of additional PET deployment, in addition to the existing centres in Québec, could vary from several tens of millions of dollars to more than about $100 million, depending on the sites chosen (leaded vaults, etc.) and the proposed number of scanners and cyclotrons.

The variables in terms of equipment cannot, however, be disassociated from the human resources variables, and the issue now is mainly no longer just the number and location of the scanners and cyclotrons required to meet the needs of the Québec population in the short term, but also how many dedicated scanners could be operational in the short term, given the specialized physical and human resources needed for the clinical use of PET.

It should be borne in mind that the human resources requirements for PET utilization are a function of the technological features that are specific to it. Thus, the use of positron-emitting tracers that have to be produced near or even on the premises requires personnel capable of operating cyclotrons, extracting the radioisotopes that are generated, incorporating them into products for human use, ensuring their quality and transport, performing scans, and lastly, correctly interpreting the results. In other words, operating a PET centre equipped with scanners and a cyclotron requires a team trained specifically in PET consisting of radiophysicists, radiochemists, radiopharmacists, nuclear medicine technicians and nurses, and nuclear medicine physicians.

Although we are unable to present accurate data on the available manpower other than that at the existing centres, specifically in terms of specialized human resources, we can say that there is currently a shortage of such resources and that this shortage would become apparent if scanners and cyclotrons were installed at new, clinically oriented sites in the short term. The training of specialized personnel becomes as limiting a factor as providing space and purchasing equipment. Self-training in this high-tech area does not seem to be a very feasible solution.

One possible approach for facilitating the deployment of PET in Québec might be to give the centres that are already equipped with PET an explicit mandate to train the specialized personnel needed to operate future PET centres. This would reduce the current need to obtain such training outside Québec. The clinical service output capacity at these centres should be bolstered in order to carry out this mandate.

It would also be advisable to plan the best scenarios for providing other university hospital centres and university institutes with the facilities and human resources needed to offer clinical PET services. Whatever the scenarios, they should be part of a deployment strategy based on meeting the population's needs and centred on cooperation between the different sectors and the implementation of quality standards.

In short, because of the operational and administrative aspects to be taken into consideration when deploying PET in Québec, and this beyond simply recognizing its clinical efficacy, a ministerial master plan should govern this deployment, taking into account the population's clinical needs and the specialized human and physical resources required by this technology.

7. CONCLUSIONS AND RECOMMENDATIONS

7.1 CONCLUSIONS

- Because of its ability to provide information on both the anatomical location of tissues and their functional dynamics, PET makes an important contribution to medical imaging.
- Recent, structured assessment reports and *AÉTMIS's* update on works published after these reports lead to the conclusion that, at this time, although there are still few hard comparative study data on PET's clinical performance, they are sufficient to support the recognition of various clinical applications in oncology, cardiology and neurology.
- The reports underscore the paucity of data on the cost-effectiveness of this technology. However more-recent economic studies and the models performed by *AÉTMIS* and adapted to the situation in Québec suggest that PET could prove to be efficient in managing patients with non-small-cell lung cancer and in myocardial viability studies. These findings are still hypothetical and require further examination with more-complete, validated data. As for uses other than the two mentioned here, PET's efficiency in the Québec context is still not known, as is the case for most other health-care systems.
- More than one payer already covers certain clinical applications of PET, which increase in number each year. The conditions governing reimbursement vary both according to the organization and the application. These restrictions reflect these organizations' eagerness to contain the use of PET on a first-recourse basis for unrecognized applications and to generate data that can further document the context of recognized uses.

The clinical uses examined thus far are, to a large extent, based on diagnostic performance or therapeutic guidance criteria, not on the measurement of effects on patient survival or quality of life. Despite these limitations, the efficacy of PET in clinical applications seems sufficiently documented and promising to increase the Québec population's access to it.

7.2 RECOMMENDATIONS

Deployment

- Since the clinical efficacy of PET is recognized for many oncological, cardiological and neurological applications, it would be advisable to promote and support, in Québec's public health-care system, the deployment of this technology for clinical purposes.
- PET scans should be performed first for clinical applications with recognized clinical efficacy. These applications should be reviewed periodically as new hard data reflecting rapid changes in the relevant information become available.

Deployment Specifics

- A master plan for deploying PET should be prepared by the Ministère de la Santé et des Services sociaux.
- The plan should include quantifying the population's PET scan needs, both with regard to optimizing the other existing technologies and to the requirements for PET for which human and physical resources might sometimes prove to be a limiting factor. The plan should therefore be prepared both in collaboration with the existing PET centres, whose expertise can be used to good advantage, and with the different key players in tertiary intervention settings.
- The plan should take into account the fact that PET cannot be deployed for clinical purposes without conducting research into promising applications that are presently recognized as potential uses but whose efficacy and cost-effectiveness have not yet been demonstrated.
- Since the plan should include an evaluation of the efficiency of PET while it is being deployed for clinical purposes, the plan should be carried out in close collaboration with university hospital centres and university institutes.

* * * * *

Appendix 1

Technical Data on PET

APPENDIX 1: TECHNICAL DATA ON PET

A1.1 EQUIPMENT FOR PRODUCING POSITRON-EMITTING RADIOISOTOPES

The main principles of interest in positron-emission tomography can be divided into two categories according to the method of production: isotopes produced by a cyclotron and those produced by a generator.

Isotopes produced by a cyclotron

Oxygen-15	(^{15}O)
Fluorine-18	(^{18}F)
Nitrogen-13	(^{13}N)
Carbon-11	(^{11}C)

All four of the main isotopes produced by a medical cyclotron are used for clinical applications of PET or for its routine research applications. Of these, fluorine-18 (for labelling FDG) suffices for all the current clinical uses in oncology. The advantage of fluorine is that it can be delivered to locations far from the production site. In oncology, the other isotopes are used for research. In cardiology, however, nitrogen-13, oxygen-15 and carbon-11 have direct usefulness in clinical (and clinical research) applications.

A cyclotron is a particle accelerator that accelerates ions (in general, the new cyclotrons used in medicine accelerate a proton that has two electrons (an H^-, i.e., a negatively charged hydrogen atom) to transform an isotope (nonradioactive) into a radioactive isotope. For example, to produce ^{18}F, one generally bombards about 1 to 2 mL of $H_2{}^{18}O$ (which costs about $250/mL) with a beam of protons for the reaction $^{18}O(p,n)^{18}F$. The proton strikes the nucleus of the oxygen-18 atom, and a neutron is expelled. The new atom, whose nucleus contains excess protons, becomes radioactive. The protons come from the beam of hydrogen atoms, since their electrons are removed before reaching the target.

Cyclotrons come in different sizes:

< 5 MeV	Dedicated to the production of oxygen-15 only (research).
10-13 MeV	Can produce the four common isotopes with good yields. This is the type of cyclotron installed most often in hospitals.
17-19 MeV	The output is generally higher (can serve several hospitals). The option of a deuteron beam on these models reduces the cost of producing ^{15}O if research studies in neurology and psychiatry are a priority. In general, these cyclotrons are more versatile for producing isotopes used less frequently in research, such as iodine-124, copper-64 and bromium-76.
≥ 30 MeV	These cyclotrons are used for the commercial production of isotopes for conventional nuclear medicine (Tl-201, I-123, In-111, etc.), but they can also produce the four isotopes commonly used in PET. These instruments are necessary only in situations where they are justified economically by the commercial need for conventional isotopes in nuclear medicine.

The purchase price of a cyclotron usually depends on its accelerating power (10-19 MeV), the number of targets (each target produces one isotope), the number of irradiation ports (1 or 2), the option of deuteron acceleration, the shielding (partial, complete or none) and the option of varying the beam energy. It also depends on the facilities required for labelling compounds for medical use (such as FDG) with isotopes (such as fluorine-18). The process of selecting a cyclotron is a complex one that requires an accurate needs assessment and special expertise in this field.

Isotopes produced by a generator

Gallium-68
Rubidium-82
Copper-62

A generator is not an instrument or a machine. It is a concept based on the disintegration of certain long-half-life radioactive isotopes into radioactive isotopes with shorter half-lives. A classic example is the ^{99}Mo/^{99m}Tc generator, which is used in all nuclear medicine departments. Molybdenum-99, which has a half-life of three days, disintegrates into Tc-99m, which has a half-life of six hours. Since the chemical properties of Tc-99m are different from those of Mo-99, they can be separated. Thus, by delivering, each week, a ^{99}Mo/^{99m}Tc generator system, one can provide, Tc-99m to departments of nuclear medicine on a daily basis. The ^{68}Ge/^{68}Ga generator is used in PET in sealed sources or cylinders for certain quality controls. ^{68}Ge does not emit positrons, but its degradation product, ^{68}Ga, does. With the half-life of ^{68}Ga approaching nine months, one can purchase, once a year, a ^{68}Ga production source that can last one year. Thus, the lifespan of a generator depends on the half-life of the parent atom. Isotopes produced by generators are usually heavier atoms that are not easily incorporated into compounds of biological interest and are therefore of limited interest.

Rubidium-82 can be used in place of nitrogen-13 for cardiac perfusion studies. Rb-82's short half-life permits shorter studies than nitrogen-13, but the images are of considerably lesser quality. However, the diagnostic reliability is the same. The cost of a commercial generator is about $40,000, and it needs to be replaced every month. Some centres build their own generators. In such cases, the cost can drop to about $8,000 a month.

Gallium-68 and copper-62 presently have no validated clinical uses, but, in the long term, new diagnostic agents may be developed from these isotopes.

Thus, a generator cannot, under any circumstances, replace a medical cyclotron for producing isotopes of interest in PET. Currently, the only clinical use of a generator is the utilization of Rb-82 for perfusion and viability studies in PET, as an addition to FDG, for facilities that do cardiology and that do not have access to short-half-life isotopes.

Positron emission tomography differs by its imaging principle, which is based on the detection of two gamma rays emitted simultaneously. Tomography in conventional nuclear medicine (single-photon emission computed tomography [SPECT]) is based on a different principle: a single gamma ray is emitted, and a lead collimator (the counterpart of an optical lens in a camera) serves to identify the ray's origin. While PET images the photons emitted by positron emitters (^{18}F, ^{15}O, ^{13}N, ^{11}C), SPECT images the photons emitted by gamma emitters (^{99m}Tc, ^{131}I , ^{201}Tl, ^{111}In, ^{67}Ga). The radioactive atoms used in SPECT are heavier and generally do not permit a direct measurement of biochemical processes in the human body. One cannot label deoxyglucose with iodine, for example, and preserve its biological properties.

SPECT scanners cannot image positron emitters without unacceptable compromises in image quality (Section A1.1.1). Some SPECT scanners are equipped with hybrid circuits that enable them to detect the two photons emitted simultaneously (Section A1.1.2).

There are several types of instruments designed for positron emission tomography. These instruments (PET scanners or PET cameras) are to be distinguished from cyclotrons, which produce radioisotopes. A PET scanner consists of detectors (made of scintillating crystals) coupled to photomultiplier tubes and of an electronic signal amplification and processing device. The scintillating crystal is a key determining factor of a PET scanner's performance, but other aspects, such as the geometric configuration and the underlying electronics, also determine an instrument's clinical performance. The detection principle in PET is based on the emission of one positron per radioactive atom. The positron travels a very short distance (1/10 of one millimeter) before annihilating, emitting two gamma rays in opposite directions. Since two rays are emitted at 180°, detecting this radiation does not normally require the addition of collimators (lead lenses), as in conventional nuclear medicine. The detection sensitivity (percentage of radiation emitted by the patient that is picked up by the PET scanner) is thus higher than in conventional nuclear medicine. The spatial resolution (the instrument's ability to visualize small lesions) is also very good (typically 4.5 to 5.5 mm).

Technical parameters apart from sensitivity and spatial resolution are important as well, such as the peak noise-equivalent count rate, which indicates the instrument's ability to process a large amount of information at the same time. The crystals used in dedicated or hybrid PET scanners generally consist of BGO or NaI(Tl). As of this year, new scanners are equipped with detectors containing better-performing crystals (LSO and GSO), but their availability is still limited.

There are three main categories of instruments that can be used for detection in PET:

A1.1.1 Shielded conventional nuclear medicine camera equipped with a high-energy collimator (511 keV)

Since a heavy lead collimator masks more than 95% of the radiation emitted by the patient, this approach has been rejected for imaging in oncology, since tumors smaller than 3 cm cannot be detected. In cardiology, some publications report success with this approach for evaluating myocardial viability.

A1.1.2 Collimator-less hybrid nuclear medicine camera for detecting coincidence photons

These systems use nuclear medicine gamma cameras, to which shielding, a thicker crystal and special electronics for detecting the photons emitted in coincidence upon the positron's annihilation have been added. This option increases the cost of a new gamma camera by about $250,000. Some recent cameras can sometimes be retrofitted with this option. This requires certain compromises in the quality of conventional nuclear-medicine studies. Most of the existing equipment in Québec cannot be upgraded for this technology. This approach was developed for centres with a very small potential number of patients requiring PET scans. In theory, the spatial resolution is excellent but in practice is poor: these scanners' peak noise-equivalent count rate is so low that the injected dose has to be decreased or extra lead filters have to be added to prevent the others from becoming saturated. The scans take a long time, and lesions smaller than 2 cm are often not detected. Since many of these scanners cannot adequately correct for the absorption and scattering of the rays by the patient's tissues, the studies are nonquantitative. Cardiac studies are possible only on scanners equipped with coincidence attenuation correction (presently, the minority). These scanners may be useful for certain applications (evaluating a residual mass or pulmonary nodules ≥ 2 cm) when the anticipated volume of activity cannot justify the purchase of a dedicated PET scanner. The literature still provides too little support to justify the wide-scale use of these scanners. This is why the Health Care Financing Administration (which administers Medicare in the United States) has not approved coverage of new uses for scans performed with these instruments.

A1.1.3 Dedicated PET instruments

These scanners are fully dedicated to PET imaging. They are generally suitable for clinical use, but their features vary. The more expensive ones are more versatile for research applications, while the less expensive ones are generally somewhat more limited to routine clinical use. There are several types of dedicated instruments:

A1.1.3.1 Partial-ring scanners

These instruments are equipped with partial detector rings, which reduces the construction costs, but a full ring can be simulated by rotating banks of detectors. The detection sensitivity is lower than that of the other scanners that are currently available but is the same as that of the scanners that have been used in most of the clinical trials published to date.

A1.1.3.2 NaI(Tl) full-ring scanners

These scanners use full rings but large, curved or rectangular crystals. They have a high detection sensitivity, good spatial resolution and a peak noise-equivalent count rate suitable for oncology but are of more limited use for research applications in cardiology and neurology, which require a very good count rate performance. These scanners' performance in oncology imaging is generally equivalent to that of multidetector scanners, but they are less versatile. They are less expensive.

A1.1.3.3 Full-ring multidetector scanners

Instead of using large crystals, these scanners use matrices of small, individual crystals. In general, they have a better peak noise-equivalent count rate, which is not essential in clinical oncology imaging, but which may be necessary in several research and cardiology applications. These instruments' performance varies according to the size of the crystals and the processing electronics. Their cost generally depends on the number of crystals.

A1.1.3.4 PET scanner coupled to an axial CT scanner

Several prototypes have been announced or are available. They are PET scanners coupled to a CT scanner. Computed tomography is used for anatomical localization and to make certain image corrections. These systems are expensive, costing $500,000 to $1 million more than a dedicated multidetector PET scanner. The ability to directly merge images is an attractive one for certain applications, such as planning radiation therapy for oncology patients, but evaluative research still needs to be conducted to determine the incremental benefit of integrated computed tomography in relation to a PET study performed separately.

A1.1.3.5 Scanner with GSO and LSO crystals

Two scanners are now commercially available (or will be in the next few months). Within the next few years, it is expected that most PET scanners will be using these better-performing crystals. These scanners should reduce PET scan length by one half and therefore considerably improve patient flow, without scan quality being affected. Their cost will probably be close to that of a top-of-the-line, dedicated, multiple-crystal scanner. Their performance characteristics have not yet been published.

A1.2 SAFETY

The recent Australian report [Medicare Services Advisory Committee (MSAC): Ghersi et al., 2000] summarizes the available information. PET is a noninvasive diagnostic procedure whose safety is generally recognized. Safety-related issues mainly concern the radiopharmaceuticals rather than the procedure as a whole.

A retrospective study [Silberstein et al., 1998] was conducted at 22 PET centres in the United States in order to determine the prevalence of adverse reactions to positron emitters, mainly ^{18}F-fluorodeoxyglucose (FDG), but also ^{11}C-CO_2, ^{11}C-methionine, ^{13}N-NH_3 and ^{15}O-H_2O. The centres provided retrospective data that had been gathered from when they had opened up to 1994 and monthly prospective data gathered between 1994 and 1997. The data concern 33,295 retrospective doses and 47,876 prospective doses, for a total of 81,801 doses of positron-emitting radiopharmaceuticals. No adverse reactions to these some 80,000 doses were reported or observed, with a 95% confidence interval of 3.7 per 100,000 doses.

According to this large prospective study, the safety of the radiopharmaceuticals used in positron emission tomography is well documented and seems very high. The *United States Pharmacopeia - Drug Information* [USP DI, 1998] also states that there are no known adverse reactions associated with the use of FDG. Since the radiotracers are usually used in microgram amounts, the incidence of adverse reactions to these very small quantities of labelled substances is very small.

The available information on the distribution of PET centres in Europe and North America and on the number of PET scans per year per population is provided in Appendix 3.

There are no absolute contraindications to a PET scan. Claustrophobia is seldom a problem (< 0.5%). In very severe cases, one must forgo the examination. This problem is more pronounced with PET/CT systems, where the patient is placed in a long tunnel, as in MRI. Very obese patients (> 158.5 kg) cannot be scanned.

A1.3 PRE-PET SCAN PATIENT PREPARATION

Typically, a PET scan consists of transmission images and emission images. Transmission images are used to correct emission image data for the attenuation effects of soft tissues and to align different emission images (from the same or a different session). The images can be interpreted visually or semiquantitatively. Two semiquantitative parameters commonly used are the standardized uptake ratio (SUR) and the lesion-to-background ratio [ICSI, 2001].

A1.3.1 Oncology studies

Patients need to be in the fasting state during the six hours preceding the scan. However, they are encouraged to drink water in order to maintain good hydration, and they may take their usual medications. Fasting is necessary in order to keep the plasma glucose and insulin levels as low as possible. A high glucose level competes with FDG and thus reduces tumor uptake. A high insulin level promotes uptake of the tracer by the muscles and heart at the expense of tumor uptake.

Precautions should be taken for diabetic patients. It is advisable to reduce their blood glucose level with intravenous insulin before injecting FDG. Since the insulin level should be low when FDG is injected, it should always be injected at least one hour after the last dose of intravenous insulin.

Some very tense patients require the administration of a benzodiazepine before FDG is administered, in order to prevent strong muscle uptake, which occurs near the neck, axillae and greater supraclavicular fossae. At many centres, patients scanned for neck cancer systematically take benzodiazepines to prevent these artifacts.

A1.3.2 Brain studies

The initial preparation is the same as for oncology studies, i.e., fasting and glycemic control.

A1.3.3 Cardiac studies

Rest perfusion
No special preparation is required.

Stress perfusion
Patients must be in the fasting state.

Myocardial viability
Unlike in oncology studies, FDG cardiac uptake is desirable.

Patients need to eat a light meal in the morning of the PET scan. Upon their arrival, nondiabetic patients receive sweetened juice (oral glucose load) containing 25 to 75 grams of glucose. One hour later, FDG is administered, together with a small dose of insulin, if need be.

Diabetic patients should be stabilized by means of a long procedure consisting in administering a supraphysiologic concentration of insulin by infusion and in stabilizing the blood glucose level with a second infusion with a dextrose solution. This procedure, referred to as "euglycemic-hyperinsulinemic clamp", takes 90 to 120 minutes.

A1.4 ROUTINE CLINICAL PROCEDURES USED DURING PET SCANNING

A1.4.1 Oncology studies

The radiotracer used in oncology studies is ^{18}FDG. It is administered to the patient via an intravenous catheter introduced into a vein in the arm. Direct intravenous injection should be avoided, since it could result in an artifactual accumulation of the substance in the axillary lymph nodes. The injection is done outside the PET scanning room. An hour later, the patient is placed in the scanner, lying face up, preferably with the arms folded above the head or, if the patient is uncomfortable doing this, alongside the body. Obtaining images generally takes between 45 and 60 minutes, depending on the patient's size and the extent of the examination.

Since FDG is excreted by the kidneys and accumulates in the bladder, it is occasionally necessary to obtain additional images of the pelvis, after administering a diuretic. This dilutes and eliminates urinary activity and permits a better evaluation of the perivesical region, which would otherwise be masked by a significant accumulation of FDG in the bladder. This requires an extra imaging session, which takes about 90 minutes. Ovarian, cervical, colon, rectal and bladder cancers and lymphoma may frequently necessitate this procedure.

A1.4.2 Brain studies

The radiotracer used in brain studies is ^{18}FDG. Images are taken 45 minutes after it is injected. The scanning takes between 15 and 30 minutes.

A1.4.3 Cardiac studies

Perfusion (rest and stress)

$^{13}NH3$, ^{82}Rb or $H_2{}^{15}O$ can be used as the radiotracer.

An intravenous catheter is introduced into a vein in the arm, and the patient is positioned, prior to injection, in the scanner. Positioning the patient is a delicate operation and can take 10 to 15 minutes. Dynamic acquisition begins at the same time as the injection and lasts for a total of 20 to 30 minutes.

The procedure for stress perfusion is the same as that for rest perfusion, but the agent is injected after the administration of a myocardial stress agent, such as dobutamine, adenosine or dipyridamole.

A1.4.4 Glucose metabolism studies

^{18}FDG is used as the radiotracer.

The radiotracer is injected 45 minutes before image acquisition, when the patient is outside the scanning room. The patient is positioned in the same manner as for a perfusion study. Image acquisition takes 20 to 30 minutes. A myocardial viability study always consists of two parts: a rest perfusion study and a glucose metabolism study. Both are usually performed on the same day.

Appendix 2

Radiation Protection in the Positron Emission Tomography (PET) Laboratory

APPENDIX 2: RADIATION PROTECTION IN THE POSITRON EMISSION TOMOGRAPHY (PET) LABORATORY

A2.1 INTRODUCTION

The problem of radiation protection is very different in a PET laboratory than in a conventional nuclear medicine department, mainly because of the very short half-lives of the radioisotopes used in such a laboratory.

Four radioisotopes are used at the laboratory of CHUS's Clinical Research Centre (CRC). The isotopes in question are listed in the following table, together with their half-lives.

Table 8: Cyclotrons products

PRODUCT	HALF-LIFE
^{11}C	20 minutes
[C-11]CO_2, [C-11]CO, [C-11]CH_3I	
[N-13]ammonia	10 minutes
^{15}O	2 minutes
[O-15]H_2O, [O-15]CO_2, [O-15]CO, [O-15]O_2	
^{18}F	110 minutes
[F-18]F_2, [F-18]F^-, [F-18]-L-DOPA, [F-18]FDG	

These isotopes are created by specific chemical reactions that take place during the collision of electrons with targets consisting of various stable substances, as indicated in Tables 9 and 10.

The production yield varies from 70 to 90%, depending on the parameters used and the purity of the target that undergoes bombardment.

Table 9: Nuclear reactions for producing radioisotopes

RADIOISOTOPE	NUCLEAR REACTION	TARGET
Carbone-11	$^{14}N[p,\alpha]^{11}C$	^{14}N - Nitrogen
Nitrogen-13	$^{16}O[p,\alpha]^{13}N$	$H_2{}^{16}O$/Ethanol solution
Oxygen-15	$^{15}N[p,n]^{15}O$	^{15}N - Enriched nitrogen
Fluorine-18 [^{18}F]F_2	$^{18}O[p,n]^{18}F$	$^{18}O_2$ - Enriched gas
Fluorine-18 [^{18}F]F^-	$^{18}O[p,n]^{18}F$	$H_2{}^{18}O$ - Enriched water

Table 10: Radioisotope production parameters

TARGET	REACTION	CURRENT	BOMBARDMENT TIME	RESULTING ACTIVITY
^{14}N	$^{14}N[p,\alpha]^{11}\mathbf{C}$	40 µA	40 min	1,500 mCi
^{16}O	$^{16}O[p,\alpha]^{13}\mathbf{N}$	20 µA	20 min	800 mCi
^{15}N	$^{15}N[p,n]^{15}\mathbf{O}$	30 µA	6 min	1,000 mCi
^{18}O	$^{18}O[p,n]^{18}\mathbf{F}$	40 µA	40 - 60 min	1,000 mCi

A2.2 REQUIRED LICENSES

For a PET centre to be able to operate properly, it needs several licenses from the Canadian Nuclear Safety Commission (CNSC). To begin with, a license to use a cyclotron is required, if the centre has one. It is a class II nonmedical particle accelerator operating license, which authorizes the holder to produce, use, dispose of and distribute radioisotopes.

The use of these radioisotopes also requires a utilization license, which authorizes the holder to possess, use, dispose of, store, distribute and import radioisotopes whose total activity exceeds 10 GBq. A list of the radioisotopes used must appear on the license.

Distributing radioisotopes to other centres requires support from all those involved at the distribution centre and the user centres. The transport distance between the distribution centre and a user centre should be factored into the radioisotope production process. The radioisotope's physical half-life is used to calculate the activity to be generated. It is generally agreed that the transport time between the two centres should not exceed two half-lives. For example, ^{18}F and ^{18}FDG, in liquid form, can be transported between two cities more than 100 km apart. On the other hand, the isotopes ^{11}C, ^{13}N and ^{15}O cannot be transported from one city to another because their half-lives are too short. One would have to produce a very large quantity of isotope in order to obtain the very small amount needed. This is especially the case with the latter two isotopes, which cannot be transported from one floor to another within a given building.

A2.3 THE PERSONNEL REQUIRED

1. Cyclotron laboratory personnel.
    - The person who operates the cyclotron that produces the radioisotope ($^{18}F^-$).
    - A radiochemist for collecting the product of the cyclotron ($^{18}F^-$) and for synthesizing the radiotracer (FDG).
    - A radiopharmacist for purifying the synthesized radiotracer (FDG) and for its quality control.
2. A nuclear medicine specialist, who contacts the user centre and determines the total amount to be shipped.
3. A radiation protection supervisor, who oversees the procedures for producing and packing the product to be shipped.
4. A carrier accredited by Health Canada and the CNSC. The carrier must have a license in due form for transporting radioisotopes.

5. A nuclear medicine specialist at the user site, who supervises the receipt of the package and conducts leak tests.

A2.4 PACKAGING FOR THE RADIOISOTOPE

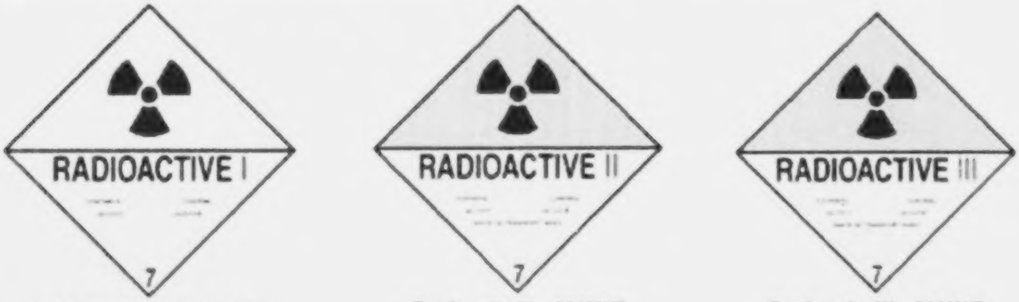
The radioisotope must be transported in a type A package, which can be a cardboard or wooden box or a metal drum. The package must have been manufactured in accordance with engineering standards. The general features of the package are as follows:

- The minimum edge length is 100 mm.
- The package must be sealable.
- The outside surfaces must be smooth and free of protrusions, unless they are for transporting the package.
- The package must the able to withstand a wide range of temperatures (70°C to -40°C).
- It must be resistant to breakage and cracking if the temperature is outside the safety range.
- It must be able to retain the radioactive contents if the ambient pressure drops to below 25 kPa.
- The package must contain enough absorbent material to contain more than twice the volume of radioactive liquid being transported (**≤ 50 mL**) in the event of a leak in the package's inner container.
- The outer package must have more than twice the volume of the radioactive liquid being transported (> **50 mL**) in the event of a leak in the package's inner container.

A self-adhesive radioactive label indicating the isotope being transported, its activity and its transport category must be placed on the package. There are three types of self-adhesive labels:

- Radioactive I: The radiation level does not exceed 5 μSv/hr anywhere on the external surface of the package.
- Radioactive II: The radiation level does not exceed 500 μSv/h anywhere on the external surface of the package. Transport index ≤ 1.
- Radioactive III: The radiation level does not exceed 2,000 μSv/h anywhere on the external surface of the package. Transport index ≤ 10.

Figure 1: Categories of radioactivity



Categorie I - BLANCHE

Categorie II - JAUNE

Categorie III - JAUNE

A2.5 RADIOISOTOPE DISTRIBUTION DOCUMENTS

The radioisotope distribution centre must have a certain number of important documents. They include the following:

- The procedure for packing the radioisotopes produced.
- A license to possess, import, use, store and dispose of the radioisotope received (^{18}F as ^{18}F- or ^{18}FDG) or radioisotopes whose atomic number is between 1 and 89. The license is issued by the CNSC.
- A license to transport high-activity radioisotopes, which is issued to the carrier by the CNSC.
- The carrier's emergency procedures in the event of an accident.

A2.6 PROCEDURE FOR PREPARING RADIOACTIVE PACKAGES

The packing procedure comprises five important steps. They may be supplemented by additional verification procedures, at the facility's discretion. The five steps are as follows:

Step 1: Check the package for contamination

- Measure the radiation level with a gamma counter.
- Perform a dry-smear test on the internal and external surfaces of the inner package and on the external surface of the outer package.
  - No contamination is allowed on the inner package.
  - Allowable fixed contamination on the outer package: ≤ 0.5 µSv/h at 0.5 m (***higher fixed contamination means reduced activity***).
  - Allowable nonfixed contamination on the outer package: ≤ 0.5 Bq/cm_ on a surface of 100 cm_ (*test performed with dry cotton*).

Step 2: Check that it is a type A package.

- Check that the package is not damaged.
- Check that any openings are sealed.
- Make unusable any component of the package that is not intended for its transport.

Step 3: Check that the inner vial is not contaminated.

- Perform a smear test on the outer surface of the vial. No contamination is allowed.

Step 4: Pack the vial in the inner package.

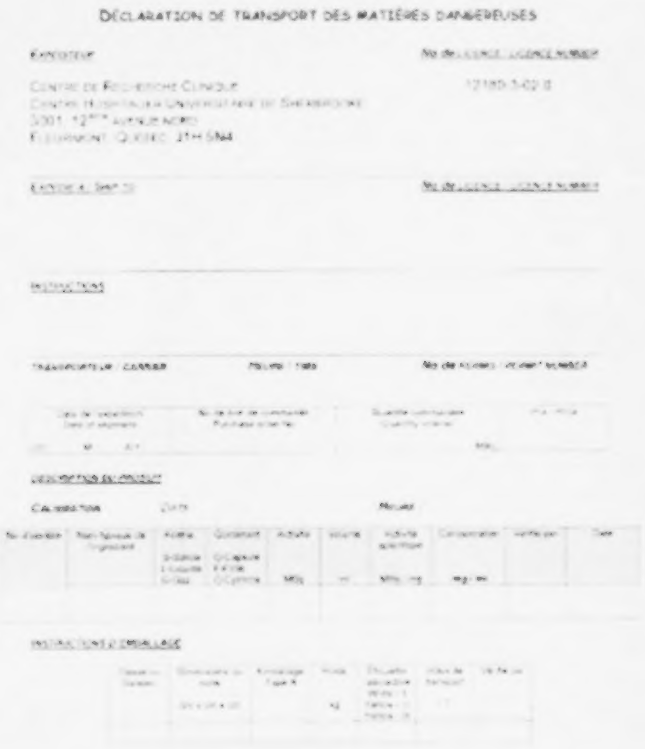
- Place enough absorbent material in the inner package to contain twice the volume of the liquid radioisotope being shipped.
- Seal the inner package.
- Perform a leak test on the surface of the inner package.
- Seal the inner package.
- Seal the outer package.

Step 5: Determine the index radiation level.

- Using a contamination counter, measure the radiation level at 1 m from the outer surface of the package. Record the value in mR/hr.

Complete the hazardous materials bill of lading. A copy accompanies the package and is given to the requesting site. Another copy is kept by the carrier. The distrubution site keeps the original copy.

Figure 2: Hazardous materials bill of lading (specimen)



DÉCLARATION DE TRANSPORT DES MATIÈRES DANGEREUSES

A2.7 THE CARRIER

The carrier must be a company recognized by the CNSC as having all the necessary qualifications for carrying out this type of transport. In Canada, two such companies that regularly do this type of transport: DUPONT and NYCOMED AMERSHAM. Companies like PUROLATOR and FEDERAL EXPRESS do general transport. It is not advisable to use such companies, since the management of emergency situations is not as well documented as for specialized companies and since the level of responsibility is not the same. Transporting radioactive materials requires special handling of the packages and specialized knowledge of radioisotopes.

A2.8 EMERGENCY PROCEDURE

A2.8.1 General emergency procedure

The first step of an emergency procedure in the event of an accident is to call 911. First-line support is provided by the local fire department. It will determine the extent of the damage and set up a security perimeter. Decontamination of the site begins quickly. A decontamination bath is set up to decontaminate anyone who may have been contaminated by the substance. The local police department is subsequently contacted, then Urgence-Santé, which provides ambulance service and contacts the emergency rooms at the local hospitals. It also contacts the regional health board, which takes charge of the overall emergency operations.

A2.8.2 Procedure carried out by a specialized carrier

First-line support is provided by the company specializing in on-the-road incidents, which is hired by the carrier. As soon as an accident occurs, the driver, if able to call the company, does so by dialing a special number at his or her disposal. The accident is managed by the specialized company. It provides the equipment and trucks required for decontamination. It also contacts the local police departments and hospitals. This emergency procedure must necessarily be approved by the CNSC through the issuance of a radioactive materials transport license. If the driver is injured to the point where he or she is unable to contact the company, the general emergency procedure is begun as soon as the call to 911 is made.

A2.9 LEVELS OF RESPONSIBILITY

The production site is responsible for the radioactive material until it arrives at its destination. Upon its arrival, the receiver contacts the distribution site in order to release the latter from this responsibility.

The carrier is responsible for providing the type A package, taking the radioactive material to its destination and taking charge of the emergency procedures in the event of an accident.

The receiving site is responsible for receiving the package and the procedure for opening it, as adopted by the CNSC. The essential steps of this procedure are as follows:

- Check the package for any damage.
- Measure the radiation level at the surface of the package. If it exceeds 2 mSV/hr, it should be assumed that there is a leak.
- Measure the radiation level at 1 m from the surface of the package in order to check the transport index.
- Perform a dry-smear test on the surface of the package, then on the internal surface in order to determine if there are any leaks.
- Report any of the following abnormalities to the CNSC and the distribution site:
    - Discovery of a leak in the package.
    - Radiation level exceeding 10 mSV/hr on the surface of the package.
    - Radiation level exceeding 200 µSV/hr at 1 m from the surface of the package.
    - Nonfixed contamination exceeding 3.7 Bq/cm_.

The distribution centre must act promptly to determine the cause of the incident and correct the situation before the next shipment. The results of the inquiry and any corrective procedure must be sent to the CNSC as soon as possible.

Appendix 3

The Geographic Distribution of PET Centres

APPENDIX 3: GEOGRAPHIC DISTRIBUTION OF PET CENTRES

Table 11: Geographic distribution of PET centres

(1999 to 2001, depending on the source*)

Continent, country, region or province	Number of PET centres	Number of scanners: dedicated (vs. total)	Number of scanners with cyclotron (cyclotron alone)	Scanners per 1 million population	Number of PET scans reimbursed per 100,000 population by public systems (July 98 - June 99)
Africa					
Saudi Arabia	1				
North America					
U.S.		75 (120 coincidence)		0.4	17.8
Canada	(6):	8		0.2	
Québec				*0.3*	(Québec) 3.3
Montréal	1		1		
Sherbrooke	1		1**		
Ontario				*0.3*	
Hamilton	1		1		
Ottawa	1		1		
Toronto	1		1		
British Columbia				*0.3*	
Vancouver	1		1		
Alberta (2001)					
Asia					
Japan	20	37		0.3	
China	1	12		0.01	
Korea	1				
Israel	1				
Taiwan	1				
Europe					
Germany	22	35 (73)	16 (2)	0.9	
UK	6	7 (11)	5	0.2	
Belgium	7	5 (9)	5	0.9	
Russia	1	2 (9)	2	0.1	
Italy	7	8 (9)	7 (1)	0.2	
France		4 (7)	4	0.1	
Austria	2	2	1		
Czech Republic	1	1	1		
Denmark	2	2	2		14.2
Finland	4	2	2		3.6
Hungary	1	1	1		
Holland	1	3	2		0.3
Norway	1				
Spain	2	3	2		(Basque Country) 6.5 (Madrid) 0.4
Sweden	4	2	2		
Switzerland		3	3		17.2
Oceania					
Australia	4				9.7
New-Zealand					0.2

* Sources: Tashiro et al., 2001; Ghersi et al., 2000; Adams et al., 1999; and Beanlands et al., 1999.

** One additional scanner was installed at this centre in February 2002.

Table 12: Clinical use of PET at CHUS

For the period from May 15, 2000 to May 11, 2001: 1,253 scans

Lung cancer:	33.4%
Lymphoma:	21%
Breast cancer:	6.6%
Brain studies:	6.4%
ENT cancer:	5.4%
Cancer of the colon and rectum:	4.9%
Gynecologic cancers:	4.9%
Cardiac studies*:	2.5%
Melanoma:	2.3%
Testicular cancer:	1.8%
Other cancers:	10.8%

* A sizeable proportion (about 50%) of cardiac viability studies are performed in accordance with a research protocol (PARR-2 study [Beanlands, 2000-2001]) and are not included under the heading of clinical use.

Table 13: Number of clinical scans and waiting times at CHUS

For the period from May 15, 2000 to May 11, 2001: 1,253 scans

Mean waiting time*:	46 days
Median waiting time*:	32 days

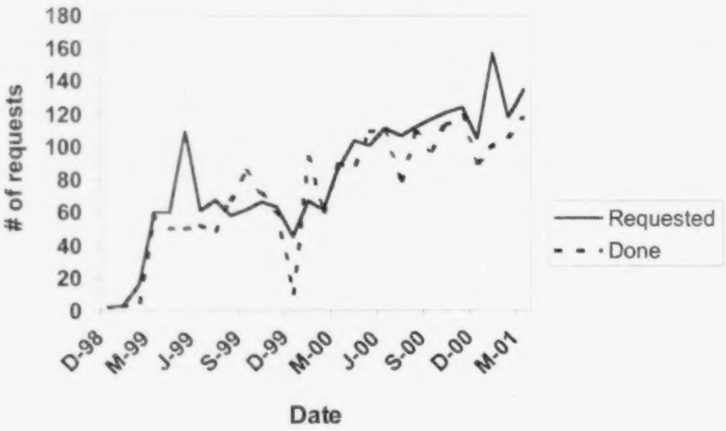
*Achieved by very effective priority management

Waiting list as at June 1, 2001: 330 patients

Table 14: Source of patients at CHUS

Hospitalized at CHUS:	172	(13.7%)
Hospitalized elsewhere:	57	(4.5%)
Outpatients (Eastern Townships):	705	(56%)
Referred from outside the E.T.:	303	(26%)

Figure 3: Growth in the demand for PET at CHUS (Sherbrooke)



Appendix 4

Location of Imaging Equipment in Québec

APPENDIX 4: LOCATION OF IMAGING EQUIPMENT (OTHER THAN PET EQUIPMENT)

Table 15: Equipment other than PET equipment by region (Québec)*

REGION	CT SCANNERS	MRI SCANNERS**	NUCLEAR MEDICINE SCANNERS
01- Lower St. Lawrence	3	1	4
02- Saguenay - Lac Saint-Jean	5	1	4
03- Québec	7	2	18
04- Mauricie and Central Québec	5	1	12
05- Eastern Townships	2	1	10
06- Montréal-Centre	28	11	62
07- Ottawa Valley	2	1	5
08- Abitibi-Témiscamingue	3	1	2
09- North Shore	2		3
11- Gaspé Peninsula and the Magdalen Islands	3		1
12- Chaudière-Appalaches	4	1	7
13- Laval	1		4
14- Lanaudière	2	1	2
15- Laurentians	2		3
16- Monteregia	8	1	10
TOTAL	77	22	147

* A detailed breakdown is provided on the following page.

** The MRI scanner will be a mobile one and will serve Region 08. In addition, in the short term, there are plans for 7 other scanners, which will bring the total number to 29.

Table 16: Imaging equipment in Québec

[Source: MSSS, December 2000; + revisions 03/01]

Location ofequipement FACILTY	Region	CT scanners	MRI scanners*	Nuclear medecine scanners
CENTRE HOSPITALIER DE MATANE	01	1		
CENTRE HOSPITALIER RÉGIONAL DE RIMOUSKI	01	1	1	1
CENTRE HOSPITALIER RÉGIONAL DU GRAND-PORTAGE	01	1		3
CENTRE HOSPITALIER DE DOLBEAU	02	1		
CENTRE HOSPITALIER DE JONQUIÈRE	02	1		
COMPLEXE HOSPITALIER DE LA SAGAMIE	02	1	1	4
PAVILLON DE L'HÔTEL-DIEU D'ALMA	02	1		
HÔTEL-DIEU DE ROBERVAL	02	1		
CHAUQ - HÔPITAL ENFANT-JÉSUS	03	2	1	2
HÔPITAL LAVAL	03	1		4
CHUQ - CHUL	03	1		4
CHUQ - HÔTEL-DIEU DE QUÉBEC	03	1		3
CHUQ - HÔPITAL SAINT-FRANCOIS D'ASSISE	03	1	1	3
CHAUQ - HÔPITAL SAINT-SACREMENT	03	1		3
CENTRE HOSPITALIER RÉGIONAL DE LA MAURICIE	04	1		2
CHETR - HÔPITAL SAINTE-MARIE	04	1	1	3
CHETR - HÔPITAL ST-JOSEPH	04	1		3
HÔPITAL STE-CROIX	04	1		2
HÔTEL-DIEU D'ARTHABASKA	04	1		2
CHUS - BOWEN BRANCH	05	1		5
CHUS - FLEURIMONT BRANCH	05	1	1	5
CHUM - HÔPITAL NOTRE-DAME	06	2	1	4
CENTRE HOSPITALIER DE LACHINE	06	1		
C.H. ANG. - VERDUN BRANCH	06	1		3
CHUM - HÔPITAL HÔTEL-DIEU	06	2	1	11
MUHS - MONTREAL CHILDREN'S HOSPITAL	06	1	1	
MUHS - MONTREAL GENERAL HOSPITAL	06	3	1	4
MUHS - ROYAL VICTORIA HOSPITAL	06	2		8
MUHS - MONTREAL NEUROLOGICAL HOSPITAL	06	1	1	
ST. MARY'S HOSPITAL	06	1		1
CENTRE HOSPITALIER FLEURY	06	1		
HÔPITAL MAISONNEUVE-ROSEMONT	06	2	1	5
CHUM - HÔPITAL ST-LUC	06	2	2	5
HÔPITAL DU SACRÉ-COEUR DE MONTRÉAL	06	2	1	5
LAKESHORE GENERAL HOSPITAL	06	1		2
HÔPITAL JEAN-TALON	06	1		
HÔPITAL SAINTE-JUSTINE	06	1	1	2
HÔPITAL SANTA CABRINI	06	1		1
MONTREAL HEART INSTITUTE	06	1		5
SIR MORTIMER B. DAVIS JEWISH GENERAL HOSPITAL	06	2	1	4
C.H. DES VALLÉES DE L'OUTAOUAIS (CHRO)	07	1	1	3
C.H. DES VALLÉES DE L'OUTAOUAIS (GATINEAU)	07	1		2
MOBILE MRI UNIT***	08		1	
CENTRE HOSPITALIER ROUYN-NORANDA	08	1		
CENTRE HOSPITALIER DE VAL-D'OR	08	1		2
CENTRE HOSPITALIER HÔTEL-DIEU D'AMOS	08	1		

Table 16: Imaging equipment in Québec (Cont'd)

CENTRE HOSPITALIER RÉGIONAL DE SEPT-ILES	09	1		2
PAVILLON LE ROYER	09	1		1
CENTRE HOSPITALIER DE CHANDLER	11			1
CENTRE HOSPITALIER BAIE-DES-CHALEURS	11	1		
CENTRE HOSPITALIER DE GASPÉ	11	1		
CENTRE HOSPITALIER DE L'ARCHIPEL	11	1		
CENTRE HOSPITALIER BEAUCE-ETCHEMIN	12	1		2
HÔTEL-DIEU DE LÉVIS	12	1	1	3
HÔTEL-DIEU DE MONTMAGNY	12	1		
CENTRE HOSPITALIER DE LA RÉGION DE L'AMIANTE	12	1		2
CITÉ DE LA SANTÉ DE LAVAL	13	1		4
CENTRE HOSPITALIER LE GARDEUR	14	1		
CENTRE HOSPITALIER RÉGIONAL DE LANAUDIÈRE	14	1	1	2
CENTRE HOSPITALIER SAINT-EUSTACHE	15	1		
HÔTEL-DIEU DE ST-JÉRÔME	15	1		3
C.H. RÉGIONAL DU SUROÎT À SALABERRY-DE-VALLEYFIELD	16	1		1
CENTRE HOSPITALIER ANNA-LABERGE	16	1		
CENTRE HOSPITALIER DE GRANBY	16	1		
CENTRE HOSPITALIER PIERRE-BOUCHER	16	1		2
HÔPITAL CHARLES-LEMOYNE	16	1	1	2
HÔTEL-DIEU DE SOREL	16	1		1
HÔPITAL DU HAUT-RICHELIEU	16	1		2
RÉSEAU SANTÉ RICHELIEU - YAMASKA	16	1		2
Total		77	22	146

Appendix 5

Description of Assessment Reports

APPENDIX 5: DESCRIPTION OF ASSESSMENT REPORTS

A5.1 COUNCIL OF MEDICAL IMAGING

The Council of Medical Imaging, an Ontario organization, conducted a literature review on positron technology [CMI: Beanlands et al., 1999]. The CMI's report was prepared for the general public and describes, in plain language, positron technology and its validated and potential applications; gives the arguments in favour of its deployment in clinical practice in Ontario; and explains the proposal for a business plan based on clinical utility and cost-effectiveness evidence for providing Ontarions with PET services. The report analyzes what PET's impact would be on the health of the population in question, with regard to improving the standard of care and cost-effectiveness, for applications in oncology, cardiology and neurology. The CMI states that its main objective would be to initiate dialogue between the interested parties on the best way for Ontario to benefit from technological advances in biomedical sciences.

A5.2 MINNESOTA HEALTH TECHNOLOGY ADVISORY COMMITTEE

In March 1999, the Minnesota Health Technology Advisory Committee (MHTAC) published a report on positron emission technology that concerns oncological applications only. The report's objectives were to evaluate, by means of a literature review, the efficacy of PET in diagnosing and monitoring cancer patients; to compare PET with other options; to assess the impact of PET on patient management and the ultimate effects on patient health; to determine the cost-effectiveness of PET in the treatment of cancer and to evaluate the effect of using hybrid PET technologies on cancer. The MHTAC's observations concerned brain tumors; cancers of the head and neck, thyroid, urinary tract and kidneys, lung, breast, esophagus, pancreas, ovaries, prostate and testicles; colorectal, neuroendocrine and gastrointestinal cancer; and melanoma and lymphoma.

A5.3 MANAGEMENT DECISION AND RESEARCH CENTER, DEPARTMENT OF VETERANS AFFAIRS -TECHNOLOGY ASSESSMENT PROGRAM (VA-TAP)

In 1996, then in 1998, the VA-TAP evaluated the experience of the Veterans Health Administration (VHA) with PET centres and conducted a systematic review of the PET literature [Flynn and Adams, 1996; Adams and Flynn, 1998]. The first assessment reported: 1) the results of systematic reviews of the clinical applications of FDG-PET for certain types of cancer (head and neck cancer, the staging of lung cancer, the evaluation of solitary pulmonary nodules, breast cancer, colorectal cancer), and for Alzheimer's disease, two important diseases in veterans; and 2) results of surveys and audits of VHA PET centres concerning the use of PET, the centres' operations, and research activities. The VA-TAP concluded that the VHA should maximize its involvement rather than set up other PET centres (implementation of a multicentre VHA PET registry, support for prospective research etc.). In 1998, the VA-TAP reevaluated the VHA's PET centres using data from the PET registries and conducted a systematic review of the PET literature published between September 1996 and December 1998 for the above-mentioned cancers and Alzheimer's disease.

A5.4 INTERNATIONAL NETWORK OF AGENCIES FOR HEALTH TECHNOLOGY ASSESSMENT

Given the increasing interest in PET worldwide, the INAHTA produced, in 1999, a report on the use of PET [Adams et al., 1999] and its coverage in various countries and a synthesis of the assessments of PET conducted by INAHTA members and three private American organizations. The report examines all PET systems (full-ring conventional scanners, new partial-ring scanners and digital SPECT scanners modified for positron emission imaging). In order to document the use of PET and its coverage, the OSTEBA conducted a survey among 12 INAHTA members (excluding those in the United States) and 8 participants in the HTA Europe project that are not members of the INAHTA, in order to obtain their annual estimates of PET research and clinical applications at private and public facilities and to obtain information on the reimbursement of PET in 1997. In 1999, the OSTEBA conducted another survey among 31 INAHTA members on the availability of public coverage of clinical uses of PET between July 1, 1998 and June 31, 1999. A different approach had to be used for the United States because of the heterogeneity of American health-care systems.

Each INAHTA member was surveyed to obtain complete evaluations of the clinical use of PET. Three private American organizations also took part in the project: the Blue Cross Blue Shield Association Technology Evaluation Center, the Emergency Care and Research Institute (ECRI) and HAYES Inc.

A5.5 BLUE CROSS BLUE SHIELD ASSOCIATION TECHNOLOGY EVALUATION CENTER

The Blue Cross Blue Shield Association Technology Evaluation Center has published assessments of FDG-PET for certain applications, including colorectal cancer, lymphoma, melanoma, pancreatic cancer, lung cancer, head and neck cancer, epilepsy and coronary artery disease. Their reports evaluate the available evidence in order to determine if the use of FDG-PET in managing patients with these types of cancer can improve health outcomes. To this end, the authors examine the subject according to the following criteria:

1) The technology must have been approved by government regulatory agencies (e.g., the FDA).
2) The scientific evidence must permit conclusions concerning the technology's effects on health outcomes.
3) The technology must improve the final health outcome.
4) The technology must be as beneficial as the recognized alternatives.
5) The improvement must be easy to reproduce outside the study.

A5.6 MEDICARE SERVICES ADVISORY COMMITTEE (AUSTRALIA)

In 2000, the MSAC published a review—aimed at determining the conditions in which coverage of PET in Australia's public health-care system should be supported—of the available evidence on the safety, efficacy and cost-effectiveness of PET. To this end, a committee consisting of experts in the fields of nuclear medicine, surgical oncology and cardiology was formed to evaluate the evidence in the literature and to provide expert opinions. The study inclusion criteria published by the VA-TAP were used, together with criteria for patient selection and for blinded comparisons, among others.

A5.7 HEALTH CARE FINANCING ADMINISTRATION (UNITED STATES)

In July 2000, the HCFA received, from Drs. Michael Phelps and Sam Gambhir, a request for acceptance of global coverage of FDG-PET. A list of 22 diseases was included with the request, and, because of the large amount of evidence submitted by the PET community, the

HCFA asked the Agency for Health Research and Quality (AHRQ) for assistance. The AHRQ had the PET submission checked by the Evidence-based Practice Centre (EPC), which concluded that the PET coverage request had not been submitted in accordance with the standards for systematic reviews, but that it was a large compilation of papers on the subject. Questions were raised as to the studies that should not have been included with the request and as to various errors identified in the data taken from the studies for the purpose of preparing the summary tables. The HCFA determined that separate systematic reviews of the literature on FDG-PET were necessary in order to issue an appropriate coverage policy.

The HCFA therefore added to this coverage request PET assessments published in 2000 by the Blue Cross Blue Shield Association, the Commonwealth Review of Positron Emission Tomography and other analyses concerning lung and esophageal cancer from the requesters' submission. The following diseases were identified for the use of FDG-PET, based on these assessments and the analysis of the papers: lung cancer, colorectal cancer, lymphoma, esophageal cancer, melanoma, head and neck cancer, coronary artery disease and epilepsy.

A5.8 COMITÉ D'ÉVALUATION ET DE DIFFUSION DES INNOVATIONS TECHNOLOGIQUES (CÉDIT)

In February 1999, CÉDIT published a progress report on its positron emission tomography project [CÉDIT: Baffert et al., 1999], with guidelines for strategic medical decision-making in the context of Assistance-publique - Hôpitaux de Paris (AP-HP). The guidelines do not constitute a validated assessment outside this context. In October 1997, CÉDIT recommended to the AP-HP the creation of a PET centre for managing cancer patients. In 1998, a series of steps were undertaken to set up a PET centre. Patients management protocols will be implemented for the following uses: lung cancer, gastrointestinal cancers, lymphoma and ENT cancers. CÉDIT is planning medico-economic studies in the areas where the literature was insufficient and a clinical research program for uses such as bile duct cancer, melanoma and pediatric cancers. A scientific committee was formed and charged with evaluating the patient management protocols and the scientific protocols and with implementing them. CÉDIT also plans to set up an organizing committee to supervise the centre's operating conditions. After an evaluation period, their observations will be used to work out the details for opening centres at other hospitals [CÉDIT, 1999].

A5.9 NATIONAL HEALTH SERVICES - RESEARCH & DEVELOPMENT (UNITED KINGDOM)

As part of the NHS R&D's technology assessment program, Robert and Milne's recommendations [1999] concerning the research priorities in the assessment of positron emission tomography were published. The specific objectives of the 3-month project were to review the knowledge regarding the clinical applications of PET (oncology, cardiology and neuropsychiatry) by consulting the literature on the topic and to identify, by means of a 3-step Delphi study, the key issues for evaluative research on PET in the United Kingdom. The results of a systematic review published by the VA-TAP in the United States in 1966 were used as a starting point for the literature review and were updated by means of searches in the MEDLINE and Cochrane databases. The results of this analysis provide an up-to-date overview of the potential clinical applications of PET in the NHS.

A5.10 ANDALUSIA HEALTH TECHNOLOGY ASSESSMENT AGENCY (AHTAA)

In February 2000, the AHTAA published a report intended as a synthesis of studies of the efficacy and effectiveness of positron emission tomography. The report is based on systematic reviews and assessment reports. The authors did a search in the INAHTA's databases, the Cochrane Library and the NHS-CRD economic evaluation databases, with emphasis on the recent publication of a joint INAHTA project [1999], the result of a collaborative effort between various agencies in the network that focused on a synthesis of previous works. One of these, a recent (1998) systematic review by the Department of Veterans Affairs - Technology Assessment Program, was considered to be of good methodological quality. It was decided to conduct a search in the primary sources only for the uses that had not been covered by the previous reviews and those for which it was thought necessary to have better information, such as the use of PET in melanoma and lymphoma.

The report is centred on decision making in Andalusia's health-care system with regard to this technology, which is in its initial phase and which will require a more thorough examination in the future.

Appendix 6

Search, Selection and Evaluation of Studies

APPENDIX 6: SEARCH, SELECTION AND EVALUATION OF STUDIES

A6.1 SEARCH

Language was not an exclusion factor, although only articles with an abstract in English or French were selected automatically. Articles in Spanish or German without an abstract in English or French were selected for future consideration, if warranted.

Retrospective literature search

> PubMed (1999-2000), Cochrane and Internet
>
> Descriptors: tomography, emission-computed fluorodeoxyglucose F18 tomography, emission-computed, single-photon: Expressions: PET, SPECT (tomography and emission computed).

The descriptors in PubMed were generated from many different references, which were grouped together for certain types of studies (*review*, *meta-analysis*, etc.). The expressions initially used were matched with expressions concerning cost and efficacy (*cost OR costs OR compar* OR efficien* OR "comparative study"[MeSH Terms] OR "cost benefit analysis"[MeSH Terms] OR "efficiency"[MeSH Terms] OR "costs and cost analysis"[MeSH Terms]*).

In addition to the MEDLINE searches, a few searches were done in Embase and Cancerlit. Also, more selective identification was achieved, thanks to the assistance of the advisory committee's members, who informed us or obtained relevant publications. The references identified were grouped together in databases created with ProCite Version 5 for Windows.

Profiles (December 2000 - February 2001)

1. Current Contents (Clinical Medicine): PET or FLUORODEOXYGLUCOSE or (TOMOGRAPHY and EMISSION) or SPECT or F-18.
2. PubMed (Index Medicus): ("tomography, emission computed"[MeSH Terms] OR "tomography, emission computed, single photon"[MeSH Terms] OR (Tomography AND emission computed)) OR "positron emission tomography"[Title Word] OR "pet"[Title Word]OR "spect"[Title Word] OR "fdg"[Title Word][ALL].
3. Cochrane: Descriptors equivalent or identical to those mentioned above were used to query the databases available on CD-ROM or on the Internet.

A6.2 SELECTION

Table 17: Study selection criteria (inclusion and exclusion)

	TYPE OF PUBLICATION	SIZE OF STUDY POPULATION	STUDIES INCLUDED	STUDIES EXCLUDED	STUDY DESIGN AND METHODOLOGY	COMMENTS
CRITERIA	Language*	≥ 10 human subjects (no animal studies) with the disease of interest	Studies using the radio-pharmaceutical 2-[^{18}F]fluoro-2-D-glucose (FDG)	Duplicate studies or studies replaced by other, more recent studies (at the same hierarchical level and whose objectives were the same) by the same institution. Studies not presenting enough information to assess the comparability of the cases and control groups, or the details of the imaging protocol, to determine if the analysis of the PET data was done visually or quantitatively, or to determine the type of quantitative analysis performed.	Patient selection criteria clearly stated. All consecutive patients eligible, based on the inclusion criteria, were included. Independent, blinded comparisons conducted with a reference standard. PET scan results had no influence on the decision to perform or not perform the reference standard. The methods for performing the test are described in enough detail for replication.	

- Language was not an exclusion factor, although only articles with an abstract in English or French were automatically selected. Articles in Spanish and German without an abstract in English or French were selected for future consideration, if warranted.

A6.3 EVALUATION OF DIAGNOSTIC TESTS

The problem of evaluating diagnostic tests, especially in medical imaging, raises a number of issues that should be addressed at the outset.

The assessment of a new diagnostic tool should be sufficiently detailed to determine the extent to which and at what cost it permits a more accurate diagnosis or more accurate staging of the disease, improves patient management and clinical outcomes, and provides information or results comparable to those of a reference standard while at the time reducing costs and inconveniences (see Fryback and Thombury's model, 1991, which is cited by many evaluators).

Formal protocols for evaluating medical imaging modalities are generally limited to comparing the new modalities' potential accuracy (sensitivity and specificity) with that of conventional signal detection-type modalities [Swets and Pickett, 1982]. A discrimination process is begun in standardized conditions, once the diagnosis is made, in order to measure the accuracy with which the various readers detect the presence or absence of the disease from the images generated by the modalities being compared. The rigorous—but often artificial—selection of cases of the "disease" and of "absence of the disease" is made independently of the imaging modalities being studied.

These protocols, like the "culture" of the scientific basis for the assessment and comparison of the performance of real-time imaging tests, are neither very well developed nor standardized. As a result, the research syntheses are based on individual studies of varying quality and with vague inclusion criteria, the results apply only to a single imaging modality, and the selection techniques make comparisons difficult. Although precautions have been expressed by a number of authors [Begg, 1983; 1986; 1987; 1988a; 1988b; 1989; Feinstein, 1989; and McMaster University Group: http://hiru.mcmaster.ca/default.htm], the quality of assessment reports on diagnostic tests is markedly lower than that of assessment reports on therapeutic modalities. Furthermore, Sackett [1991], in his book on clinical epidemiology, and the McMaster University Group, in several articles on the critical analysis of published papers, had attempted to make reader-evaluators aware of this, but the first checklists for authors of assessments of diagnostic tests have barely just been developed [STARD, 2001].

The first prospective comparisons of diagnostic performance based on clinical readings of diagnostic images, which were conducted in the late 1980s, indicated beforehand the procedures to be used to arrive at a valid result [Neal, 1995, 1996; Gatsonis, 1995; Baum et al., 1995]. Initially, the prospective clinical studies were conducted by ad hoc groups in university radiology departments. It was not until 1998 that the U.S. National Cancer Institute funded the first network of such departments for prospectively evaluating new imaging technologies in an expeditious and rigorous manner [Hillman et al., 1999: American College of Radiology Imaging Network (ACRIN) http: www.acrin.org/].

The complete assessment of given diagnostic test's performance requires at least one or, ideally, several pairs of sensitivity and specificity measures. In the past, few studies reported complete ROC (receiver operating characteristic) curves or simultaneous comparisons. Such weaknesses mean that the accuracy figures reported in a study are a function not only of the imaging technique in question, but also of test "positivity" criteria (subjective), of the case mix and of selective checks. Meta-analyses [Irwig et al., 1995; Walter et al., 1999] of several studies did not fully take the effect of these three additional, nonstandardized factors into account. Thus, the comparison of diagnostic test performance is much more prone to distortions than that of simultaneous randomized, comparative trials of different treatments.

For these reasons, no assessment including a formal meta-analysis of individual studies has so far been attempted, except to indicate the observed sensitivity and specificity rates. This report follows suit.

Table 18: Methodological quality of diagnostic accuracy and diagnostic thinking efficacy studies

A	Studies with broad generalizability to a variety of patients and no significant flaws in research methods. - ≥ 35 patients with the disease of interest and ≥ 35 patients without the disease (since this number yields 95% CIs whose lower limit excludes 0.90 if Se =1). - Patients drawn from a clinically relevant sample (not filtered to include only severe disease) whose clinical symptoms are completely described. - Diagnoses defined by appropriate reference standard. - PET (positron emission tomography) studies technically of high quality and evaluated independently of the reference diagnosis.
B	Studies with a narrower spectrum of generalizability and with only a few methodological flaws that are well described (and whose impact on the conclusions can be assessed). - ≥ 35 cases with and without the disease of interest. - More limited spectrum of patients, typically reflecting referral bias of university centres (more severe illness). - Free of other methodological flaws that promote interaction between test results and disease determination. - Prospective studies still required.
C	Studies with several methodological flaws. - Studies with small sample size. - Incomplete reporting. - Retrospective studies of diagnostic accuracy.
D	Studies with multiple methodological flaws. - No adequate reference standard for diagnosis. - Test results and determination of final diagnosis not independent. - Source of patient cohort could not be determined or was obviously influenced by the test results (workup bias). - Opinions without substantiating data.

Source: Flynn and Adams, 1996.

Table 19: Assessing the quality of individual studies: Classifications of study designs and levels of evidence

(when high-quality meta-analysis/overviews are not available)

I Randomized trials with a low false-positive (alpha) and a low false-negative (beta) error rate (high power)

- Positive trial with statistically significant treatment effect (low alpha error rate).
- Negative trial that was large enough to exclude the possibility of a clinically important benefit (low beta error rate/high power, i.e. had a narrow confidence interval around the treatment effect, the lower end of which was greater than the minimum clinically important benefit).
- Meta-analysis can be used to generate a pooled estimate of treatment efficacy across all high-quality, relevant studies and can reveal any inconsistencies in results.

II Randomized trials with a high false-positive (alpha) and/or high false negative (beta) error rate (low power)

- Trials with interesting positive trend that is not statistically significant (high alpha error rate).
- Negative trials but possibility of a clinically important benefit (high beta error rate/low power, i.e., very wide confidence intervals around the treatment effect).
- Small positive trials with wide confidence intervals around the treatment effect, making it difficult to accurately assess the magnitude of the effect.
- When Level II studies are pooled (through quantitative meta-analysis), the aggregate effects may provide level I evidence.

III Nonrandomized, concurrent cohort comparisons between contemporaneous patients who did and did not (through refusal, noncompliance, contraindication, local practice, oversight, etc.) receive treatment.

- Results subject to biases.
- Level III data can be subjected to meta-analysis, but the result would not shift these data to another level and is not usually recommended.

IV Nonrandomized, historical, cohort comparisons between currently followed patients who received treatment (as a result of local policy) and former patients (from the same institution or from the literature) who did not (since, at another time or in another institution, different treatment policies prevailed).

- Results subject to biases, including those that result from inappropriate comparisons over time and space.

V Case series without control subjects.

- May contain useful information about clinical course and prognosis but can only hint at efficacy.

Source: Flynn and Adams, 1996.

Appendix 7

Positions of Current and Potential Users, Assessment Agencies and Reimbursement Organizations According to the Clinical Use of PET

APPENDIX 7: POSITIONS OF CURRENT AND POTENTIAL USERS, ASSESSMENT AGENCIES AND REIMBURSEMENT ORGANIZATIONS ACCORDING TO THE CLINICAL USE OF PET

The assessment procedure chosen by *AÉTMIS* led to a rearrangement of the data. The reports submitted between June and September 2000 to the FMSQ's Positron Technology Committee (PTC) served as the starting point. The report by Ontario's Council of Medical Imaging (1999) was included with these reports to constitute the group called "current and potential users". For Québec, the active participation of the team from CHUS, which already has a complete PET unit (cyclotron and scanner), in the drafting of the report by the Association des médecins spécialistes en médecine nucléaire du Québec (AMSMNQ) explains the term "current" in the name of this first group.

The second group consists of the main organizations (public and private) that make PET coverage policies. In its latest report (December 2000), the HCFA responds to a request—submitted by the ICCPET (renamed the Academy of Molecular Imaging on November 29, 2000)—for global coverage of PET in oncology, but does not provide a detailed account of the request. The HCFA's recommendations, published on December 15, 2000, will nonetheless have a determining influence in the United States. The Australian committee [MSAC: Ghersi et al., 2000] explains the basis of its conclusions, and its report will serve as the main comparator. In addition, and as the only example of a private insurance company, the position of the Blue Cross and Blue Shield Association was included in this group.

A third group consists of conclusions and recommendations taken from reports published by assessment agencies. Reports from other agencies are described in Appendix 5. Their conclusions or recommendations are not stated here systematically, unless they are noteworthy.

Upon examining the decision-making processes leading to the coverage of PET scans, one can situate the positions of reimbursement organizations halfway between the structured reports of assessment agencies and the expectations expressed by current or potential users. The coverage of PET scans could, in fact, serve as an indicator of the acceptance of this technology by various health-care systems.

A7.1 ONCOLOGY

A7.1.1 Lung cancer

Table 20: Positions – Lung Cancer

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BLUE CROSS BLUE SHIELD 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
INITIAL EVALUATION OF THE PULMONARY NODULE	✿	✿	✿	✿	✿	✿	✿	✿	✿	✿	✿
INITIAL STAGING OF NSCLC	NM	NM	NM	NM	✿	✿ (staging and prognosis)	✿	✿	NM	✿	✿
DETECTING METASTASES:											
MEDIASTINAL STAGING	✿ (normal CT scan)	✿	✿	✿	✿ (+ concurrent CT)	✿	NM	✿	✿	✿	NM
DETECTING DISTANT METASTASES	✿ (except for brain metastases)	NM	✿ (before thoracotomy)	NM	NM	✿	NM	✿	NM	✿	NM
MONITORING RESPONSE TO THERAPY	✿ (radiotherapy, chemotherapy, surgery)	✿ (chemotherapy and radiotherapy)	NM	✿ (chemotherapy)	✿	✿	NM	NM	NM	✿ (+ prognosis of therapeutic response)	NM
DETECTING RECURRENCE OR RESIDUAL TUMORS	✿	✿	✿ (when conventional imaging results are equivocal)	✿	✿ (restaging)	✿	✿	✿	NM	✿	NM

✿ Clinical use recognized; ✿ Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

The members of the FMSQ's PTC and of the Council of Medical Imaging (Ontario) consider that PET offers several clinical advantages over conventional diagnostic tests. Accordingly, PET is useful in the clinical situations encountered most often when managing a patient with a pulmonary nodule or proven lung cancer: 1) the initial investigation of the pulmonary nodule; 2) the evaluation of the mediastinum when a diagnosis of neoplasia is made; 3) the evaluation of the usual metastatic sites (staging of distant metastases) when a diagnosis of neoplasia is made; and 4) the reevaluation of the chest when recurrent disease is suspected [Lacasse, 2000; CMI: Beanlands et al., 1999].

According to the AMSMNQ, the systematic use of PET during preoperative evaluations would lead to the identification of patients with inoperable lung cancer and would result in a substantial reduction in hospital costs by avoiding surgery that would prove traumatic or unnecessary to the patient. The use of PET in evaluating pulmonary nodules (instead of transthoracic biopsies and surgical excision) would also reduce costs. PET performs better than conventional investigational tools (e.g., CT-guided transthoracic biopsy) and does not cause any complications that require hospitalization [AMSMNQ, 2000].

For the ARQ, the role of PET is now well-established in lung cancer. It can help distinguish between a benign nodule and a malignant one, completes the staging and contributes to better patient selection for surgery. It also permits a better follow-up after chemotherapy and radiation therapy [ARQ, 2000].

The clinical uses of PET mentioned by the CMI are the same as the preceding ones. It adds that studies specifically concerning the costs associated with PET in lung cancer should be carried out. Even though there are no such studies, it is estimated that PET can generate several million dollars in savings a year in lung cancer for Ontario [CMI: Beanlands et al., 1999].

Assessment agencies

The INAHTA and the VA-TAP recognize PET's potential in the evaluation of non-small-cell lung cancer. However, their conclusions differ with regard to the staging of this type of cancer. The INAHTA recognizes PET's potential for this application, but the VA-TAP concludes that the evidence does not support this use. Both organizations call attention to the important need to conduct further research by way of rigorous studies comparing PET with gamma coincidence cameras, partial-ring PET scanners and conventional PET with alternative strategies [Flynn and Adams, 1996; Adams and Flynn, 1998].

The MHTAC recognizes that numerous studies have shown that FDG-PET has superior efficacy to other imaging techniques, especially computed tomography, in differentiating malignant pulmonary lesions from benign pulmonary lesions. It concludes that FDG-PET is useful for diagnosing lung cancer (primary or metastatic disease) and for detecting recurrence after treatment.

Coverage policymakers

PET has been covered by Medicare since 1998 for the diagnosis of pulmonary tumors, the evaluation of solitary pulmonary nodules and the staging of non-small-cell lung cancer. In December 2000, the HCFA concluded that there was enough evidence to support PET for the detection of residual or recurrent tumors (restaging). However, certain conditions must first be met. For the evaluation of a pulmonary nodule, a CT scan must have shown the presence of a primary tumor; the concurrent results of conventional imaging must be included in the request for reimbursement; and, when PET is combined with computed tomography and performed serially, it is not reimbursed within the 90 days following negative PET findings. As for the initial staging of NSCLC, a pathology report indicating the presence of a primary tumor must be submitted, and the PET results for the entire body must be coordinated with the results of a concurrent CT scan and of a follow-up by lymph node biopsy (the lymph node biopsy is not reimbursed if the CT and

PET scan findings are negative. It is reimbursed only in the context of a positive CT scan and a positive PET scan, a negative CT scan and a positive PET scan or a positive CT scan and a negative PET scan).

The Blue Cross Blue and Shield Association Technology Evaluation Center (BCBSA-TEC) determined, in its qualitative review, that FDG-PET meets its methodological criteria for its two main uses in lung cancer (the staging of non-small-cell lung cancer and diagnosing a solitary pulmonary nodule), provided that the PET findings can result in a change in how the patient is managed [Adams et al., 1999].

The MSAC (Australia) considers that PET is more accurate than the other, conventional imaging techniques in detecting lung cancer metastases before surgery and recognizes its increased efficacy when combined with conventional imaging. Despite the evidence of superior efficacy to that of conventional imaging, the MSAC notes that it is difficult to quantify this improvement because of the variable quality of the studies reviewed, for although it is clear that PET can provide useful prognostic information that can lead to a reevaluation of treatment in patients with non-small-cell lung cancer, there are no data for assessing the impact of this reevaluation on the final outcome [MSAC: Ghersi et al. 2000].

A7.1.2 Colorectal cancer

Table 21: Positions – Colorectal Cancer

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BLUE CROSS BLUE SHIELD 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
DIAGNOSIS	NM	NM	NM	NM	NM	NM	NM	✿	NM	NM	NM
DETECTION OF THE PRIMARY TUMOR	✿	NM	NM	✿	NM	NM	NM	NM		NM	NM
DETECTING METASTASES IN THE CONTEXT OF RECURRENCE:	✿	NM	NM	✿	✿	✿	✿	✿	NM	✿	NM
HEPATIC	✿	NM	NM	NM	✿	✿	✿	NM	✿	✿	NM
EXTRAHEPATIC	✿	NM	NM	NM	✿	✿	✿	NM	NM	✿	NM
ASSESSING OPERABILITY	✿ (by detecting metastases)	NM	✿	NM	NM	✿	✿ (during staging + postop. follow-up)	✿	✿	✿	NM
EVALUATING REGIONAL LYMPH NODES	✿	NM	NM	NM	NM	NM	NM	NM	NM	NM	NM
EVALUATING RESPONSE TO THERAPY	NM	NM	NM	NM	NM	NM	NM	✿	✿	NM	NM
DETECTING RECURRENCE	✿ (+ CT scan, if necessary)	✿ (syst. screening, supplmented by CT and/or MRI)	✿	✿	✿ (+ CT scan, if necessary)	✿	NM	✿	✿	✿	✿ (as an addition to conventional imaging)
DIFFERENTIATING A POSTOPERATIVE SCAR FROM OPERABLE RECURRENCE	NM	NM	✿	NM	✿	✿	✿	NM	✿	NM	NM
DETERMINING THE LOCATION OF RECURRENT TUMORS IN THE CONTEXT OF A RISING CEA LEVEL	✿ (when results of medical imaging are negative)	NM	✿	NM	✿ (an elevated CEA should not be the only factor for evaluating recurrence)	NM	NM	NM	✿	NM	NM

✿ Clinical use recognized; ✿ Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

Both for the members of the FMSQ's PTC and the authors of the CMI's position paper, the role of PET in detecting the primary tumor in colon cancer is not defined, with colonoscopy remaining the procedure of choice for evaluating the colon and performing biopsies of suspicious lesions. For the preoperative evaluation of regional lymph nodes, the sensitivity of PET (as well as that of computed tomography) is too low. It is for the detection of hepatic metastases that PET is most useful in colon cancer, as it enables one to resect these metastases or to avoid major surgery in the presence of generalized disease. As for detecting hepatic or extrahepatic recurrence and differentiating scar tissue from local recurrence, PET has been shown to be more sensitive than computed tomography. However, it should be noted that PET can yield false-positive results during the six months following radiation therapy, because of the inflammatory reaction [CMI: Beanlands et al., 1999; Laplante, 2000; Létourneau, 2000]. In the ARQ's opinion, PET is the best technique for detecting recurrences of colon cancer. It thus supports the use of PET for systematically screening for recurrent disease, with the addition of computed tomography or magnetic resonance imaging in order to better define the extent of the recurrence and guide the choice of treatment. This would reduce the costs associated with patient follow-up [ARQ, 2000]. The AMSMNQ states that PET is generally not indicated for systematically monitoring cancer, but that in the context of an elevated CEA and of clinical suspicion of recurrent colorectal cancer, PET proves quite useful for determining the location of the recurrence, for assessing its extent and for differentiating a recurrent tumor from postoperative scar or for assessing the tumor's resectability. The CMI (Ontario) adds that there are not enough data to determine the cost-effectiveness of PET for colon cancer in Ontario.

Coverage policymakers

Since 1999, Medicare (U.S.) has been covering PET for determining the location of suspected recurrences of colorectal tumors in the context of an elevated CEA, in the following conditions: the request for reimbursement must document the previously treated colorectal cancer and the results of a concurrent CT scan (or other diagnostic technique). In 2002, the HCFA reevaluated its position and extended the indication by lifting the restriction of an elevated CEA and now provides coverage for diagnosis and staging. It recommended coverage of PET when used to differentiate postoperative scars from recurrent colorectal tumors and for detecting hepatic and extrahepatic metastases during the initial staging of colorectal cancer before any decision has been made as to how the patient will be managed [Tunis et al., 2000].

The MSAC recognizes that PET's sensitivity is superior to that of computed tomography in detecting local recurrence and hepatic metastases but also states that it is difficult to differentiate between recurrence and postirradiation inflammation. It notes that little is known about how outcomes are affected by changing management in patients who have abnormalities that are detectable only on PET. It concludes that the increased sensitivity of PET in detecting extrahepatic metastases has a major potential impact on the decision to perform or not to perform surgery, but that the effects of this decision on survival or quality of life have still not been assessed.

The Blue Cross and Blue Shield Association (BCBSA) considers that the results are comparable from one study to another and that the final outcome is definitely improved through the use of PET in detecting metastases and assessing tumor resectability during initial staging or postoperative follow-up. As for differentiating between postoperative scar and recurrent tumor, the association does not support the use of PET.

Assessment agencies

Like most other organizations, the VA-TAP recognizes PET's potential in colorectal cancer but notes that the evidence is insufficient to support its use in managing patients with this type of cancer [Flynn and Adams, 1996; Adams and Flynn, 1998].

The MHTAC believes that if other studies can confirm the current findings, FDG-PET could prove to be a valuable tool for diagnosing, preoperative staging, monitoring response to therapy and monitoring for recurrent disease. The potential role of PET when combined with conventional imaging to confirm the presence of recurrence after treatment is recognized in the INAHTA's report.

A7.1.3 Melanoma

Table 22: Positions - Melanoma

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BCBSA 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
DIAGNOSIS	NM	NM	NM	NM	✿	NM	NM	NM		NM	✿
INITIAL STAGING	NM	✿	NM	✿	✿	NM	✿	NM		NM	✿
DETECTING METASTASES	✿	NM	✿	NM	✿	✿	✿	NM	✿	NM	NM
WHEN A DIAGNOSIS OF AN ADVANCED LESION IS MADE (CLARK III AND IV)	NM	NM	✿	NM	NM	NM	NM	NM	✿	NM	NM
EXTRANODAL METASTASES	NM	NM	NM	NM	NM	NM	✿	NM	NM	NM	NM
DURING POST-TREATMENT FOLLOW-UP	✿	NM	NM	NM	NM	NM	✿	NM	NM	NM	NM
LYMPH NODE METASTASES	✿	NM	NM	✿	✿	✿	✿	NM	✿	NM	NM
POSTOPERATIVE EVALUATION	NM	NM	NM	NM	NM	✿	NM	NM	NM	NM	NM
EVALUATING RECURRENCE	NM	NM	✿	NM	✿ (as an alternative to a gallium scan)	NM	✿	NM	✿	NM	NM

✿ Clinical use recognized; ✿ Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

Computed tomography and magnetic resonance imaging are not sensitive or specific in determining the location of melanoma metastases. FDG-PET is highly sensitive. The evaluation of the sentinel lymph node by PET is, however, debated, with preference given to sentinel lymph node biopsy as a more sensitive and more specific method [Létourneau, 2000; Laplante, 2000]. The Council of Medical Imaging (Ontario) also mentions this debate, explaining that sentinel lymph node biopsy may initially seem less expensive than PET. However, an American analysis showed that sentinel lymph node scintigraphy actually increases the costs associated with staging melanoma, given the high cost of operating rooms and because it requires several services, including nuclear medicine, surgery, and pathology personnel [CMI: Beanlands et al. 1999].

For melanoma, the AMSMNQ supports PET only for evaluating metastases when a diagnosis of an advanced lesion is made and for evaluating recurrent disease. The ARQ does not explicitly express its opinion regarding the use PET in melanoma. However, it does briefly mention its potential for becoming the test of choice for staging this disease.

Assessment agencies

Despite the keen interest in using PET in melanoma in several American health-care systems, the INAHTA and MHTAC both note that the literature reviews do not enable them to clearly establish PET's role in the management of melanoma. The VA-TAP does not mention melanoma in its analysis.

Coverage policymakers

Since 1999, the HCFA has recommended coverage of PET for evaluating recurrent melanoma, prior to resection, in the following conditions: 1) a diagnosis of melanoma; 2) inclusion of findings of concurrent conventional imaging in the claim; 3) a PET scan must be used as an alternative to a gallium scan; 4) limitation on use: coverage for PET scans is allowed no sooner than 50 days after the last PET scan or a gallium scan; and 5) full-body PET scans are covered only once during a 12-month period, unless there is a documented medical need to determine the location of a recurrent tumor during this period. In its December 2000 report, the HCFA recommended that Medicare add coverage of PET for the evaluation of metastatic lesions during staging. It does not support coverage of PET for the evaluation of lymph nodes [Tunis et al., 2000].

The MSAC (Australia) concludes that PET is more accurate than conventional imaging in detecting metastatic lesions, but that it is clearly less effective than sentinel lymph node biopsy for diagnosing micrometastatic disease. PET's role in managing patients with early metastatic disease is not clear. Long-term, randomized, comparative studies would need to be conducted before any conclusions regarding this matter can be drawn.

The BCBSA concludes that the results are concordant from one study to another. It states that, in the evaluation of patients with melanoma, outcomes would undoubtedly be improved with the use of PET to detect extranodal metastases during initial staging or the post-treatment follow-up. However, it does not support the use of PET for detecting lymph node metastases in patients who are candidates for a sentinel lymph node biopsy.

A7.1.4 Head and neck cancer

Table 23: Positions - Head and Neck Cancer

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BCBSA 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
IDENTIFYING AN UNKNOWING PRIMARY TUMOR WITH METASTASES	✿ (Cervical metastasis)	NM	NM	NM	✿ (Cervical metastasis: when the primary tumor cannot be identified with conventional imaging)	NM	✿	NM	✿	✿	NM
EVALUATING THE PRIMARY TUMOR	✿	NM	NM	NM	NM	NM	NM	✿ (PET superior to MRI but equivalent to CT)	✿	✿	NM
PREOPERATIVE STAGING	NM	NM	NM	✿	NM	NM	NM	NM	✿	NM	NM
EVALUATING REGIONAL LYMPH NODES	✿	NM	NM	NM	✿ (initial staging of cervical lymph nodes in the context of metastases)	NM	✿	NM	✿	NM	NM
EVALUATING RESPONSE TO THERAPY	✿	NM	NM	NM	NM	NM	NM	NM	✿	✿	NM
DETECTING POST-TREATMENT RECURRENCE OR RESIDUAL TUMORS	✿	✿	NM	✿	✿	NM	✿	✿	✿ (cases with negative findings on CT/MRI)	✿	NM
DISTINGUISHING BETWEEN POSTOPERATIVE SCAR AND PERSISTENT TUMOR	NM	NM	NM	✿	NM	NM	NM	NM	✿	NM	NM

✿ Clinical use recognized; ✿ Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

The members of the FMSQ's PTC believe that PET does not offer any advantage over conventional imaging with regard to evaluating the primary tumor in head and neck cancer. However, it would seem to be of benefit in patients with a metastatic cervical tumor of unknown origin, but further studies are necessary to draw such a conclusion. The use of PET to evaluate regional lymph nodes and response to treatment remains to be clarified. However, PET is useful for identifying posttreatment recurrences, with better sensitivity and specificity than computed tomography and magnetic resonance imaging [Laplante, 2000; Létourneau, 2000]

The CMI (Ontario) does not mention metastatic tumors of unknown origin but considers that PET is a useful tool for the preoperative staging of head and neck cancer and for detecting posttreatment recurrence. PET is ideal for differentiating between postoperative scars and residual tumors. The CMI also mentions a small number of studies which have shown that PET is superior to MRI in detecting recurrent ENT tumors.

The ARQ indicates that studies are underway for the purpose of determining the role of PET in ENT tumors and that it could potentially become the test of choice for detecting recurrences of such neoplasms.

Assessment agencies

The MHTAC recognizes that PET's efficacy is superior to that of magnetic resonance imaging. However, for head and neck cancer, computed tomography is equivalent to PET.

Despite its assessment of PET's potential for determining the location of the primary tumor, evaluating response to therapy or differentiating between postirradiation inflammation and posttreatment recurrence, the VA-TAP maintains that the evidence is insufficient to support the use of PET in patients with head and neck cancer. Blinded, prospective, comparative studies are necessary to assess the impact that PET would have in such patients [Flynn and Adams, 1996; Adams and Flynn, 1998].

Coverage policymakers

The HCFA maintains that the evidence is sufficient for the coverage of PET costs in cases of cervical metastases if conventional imaging has failed to detect the primary tumor. In cases where PET detects a tumor confirmed by biopsy to be the primary tumor, management of the patient would be modified, which would result in a decrease in the morbidity associated with unnecessary surgical treatment or radiation therapy. However, the HCFA states that, despite the evidence of beneficial effects associated with modifying the management of these patients, the impact of this modification on the final outcome has not yet been determined. Furthermore, the HCFA considers that PET should be reimbursed for the initial staging of cervical lymph nodes when there are metastases and for the detection of recurrent or residual tumors. Coverage therefore applies to the diagnosis and staging of head and neck cancer (except for tumors of the central nervous system and thyroid) [Tunis et al., 2000].

The MSAC (Australia) makes no mention of head and neck cancer.

A7.1.5 Lymphoma

Table 24: Positions - Lymphoma

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BLUE CROSS BLUE SHIELD 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
STAGING	✿	✿	NM	✿	✿	NM	✿	✿	✿	NM	NM
RESPONSE TO THERAPY	NM	✿	NM	✿	NM	NM	NM	✿	NM	NM	NM
POSTTREATMENT FOLLOW-UP	✿	NM	NM	NM	NM	NM	✿	NM	NM	NM	NM

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

In lymphoma, PET has comparable sensitivity to that of computed tomography but has superior specificity. Furthermore, computed tomography yields a high number of false-positive results. The advantages of PET are a one-day procedure with high resolution, better dosimetry, less intestinal activity and the fact that one can perform a quantitative analysis. In addition, FDG-PET can be used to evaluate posttreatment residual lesions with great accuracy [Laplante, 2000].

The CMI (Ontario) states that staging lymphoma usually involves multiple procedures, including bone marrow aspiration and a biopsy, a CT scan of the abdomen, pelvis and chest, gallium imaging and possibly a bone scan, all of which involve costs in excess of $3,000. These numerous procedures can be replaced with a single PET scan. Furthermore, PET often reveals a more advanced stage of disease and results in more aggressive management. PET is as useful for evaluating response to therapy as it is for staging. The CMI mentions an American study [Young, 1997] in which, with the use of PET before treatment and again after two rounds of chemotherapy for evaluating the intermediate response to therapy, the mortality rate due to lymphoma decreased by one half compared to the mean national rate. The CMI also cites a European group which maintains that the therapeutic response can be evaluated by PET after only seven days of treatment. The CMI supports the use of FDG-PET as the main tool for staging all types of lymphoma and for evaluating response to therapy.

The ARQ cites the same studies as the CMI, and its position is similar, although less explicit. The AMSMNQ also supports the use of PET for initial staging and for differentiating between a residual lymphoma and a fibrotic mass.

Assessment agencies

The MHTAC states that studies comparing ^{18}F-FDG-PET with alternative techniques obtain superior results with PET compared to computed tomography, digital ^{99m}Tc-MIBI SPECT, and ^{111}In-somatostatin scintigraphy for detecting treated and untreated lymphoma, but that the evidence is limited to a few small trials. For this reason, the MHTAC cannot draw any conclusions at this time with regard to the efficacy of PET in evaluating malignant lymphoma.

The VA-TAP does not mention lymphoma in its analysis, and the INAHTA only notes that no review based on the data gathered from

1977 to 1988 was able to determine the role of PET in this application.

Coverage policymakers

In 1999, the HCFA recommended coverage of PET for diagnosing and staging lymphoma (Hodgkin's and non-Hodgkin's), with the following stipulations: a diagnosis of lymphoma must have been made; the findings of concurrent conventional imaging must be included with the claim; the PET scan must be used as an alternative to a gallium scan; there is a limitation on use, i.e., reimbursement for PET scans is allowed no sooner than 50 days after the last PET scan or gallium scan; and full-body PET scans are covered only once during a 12-month period, unless there is a documented medical need to determine the location of a recurrent tumor during this period. This position was supported by the BCBSA, which states that there is enough evidence to support the use of PET in this application [Tunis et al., 2000].

The MSAC (Australia) does not mention lymphoma.

A7.1.6 Breast cancer

Table 25: Positions – Breast Cancer

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BLUE CROSS BLUE SHIELD 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
DETECTING THE PRIMARY TUMOR *(SPECIFIC PATIENTS)*	✿ (as an addition to mammography)	NM	✿	✿	NM	NM	NM	NM	✿	✿	NM
STAGING	✿	✿	✿	✿	✿	NM	✿	✿	✿	✿ (recurrent tumors)	NM
DETECTING LYMPH NODE METASTASES	✿ or ✿	✿ (+ internal mammary chains)	✿ (as a substitute for axillary dissection)	NM	NM	NM	NM	✿	✿	✿	NM
DETECTING DISTANT METASTASES	✿	NM	NM	NM	NM	NM	NM	NM	✿	NM	NM
RESPONSE TO THERAPY	✿	✿	NM	✿	NM	NM	✿	✿	NM	✿	NM
DETECTING RECURRENCE	NM		✿	NM	NM	NM	NM	NM	✿	✿	NM

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

The members of the FMSQ's PTC consider that PET's role in detecting the primary breast tumor is often limited to specific patients, such as those with dense breasts or fibrocystic disease, those who have undergone a first biopsy, surgery or radiation therapy, and those with breast implants, or when the mammography findings are equivocal. FDG-PET is inferior to searching for sentinel lymph nodes and to biopsy in detecting metastatic axillary lymph nodes because it does not detect micrometastases, but it is useful for evaluating an axillary mass suspected of being breast cancer and can even obviate the need for axillary dissection. It is superior to mapping in detecting osteolytic bone metastases, although it may miss certain osteoblastic lesions. PET could also prove useful in evaluating response to therapy [Laplante, 2000; Létourneau, 2000].

The CMI's thinking is along the same lines. It notes that PET plays little or no role in the diagnosis of breast cancer, with the possible exception of patients with breast implants and patients at high risk, such as those whose breasts are too dense for mammography. It states that PET plays a key role in initial staging and evaluating response to therapy.

The ARQ does not mention the detection of the primary tumor in specific patients. It does, however, mention the important role that PET plays in initial staging, evaluating response to therapy and detecting axillary lymph node metastases. It attaches special importance to the detection of metastases in the internal mammary chains, since early detection and the treatment of these metastases improves survival in these patients.

The AMSMNQ supports the following uses of PET in breast cancer: detecting recurrence, evaluating mammary masses, and evaluating lymph node metastases as a substitute for axillary dissection.

Assessment agencies

The MHTAC concludes that the preliminary data seem to favour the use of FDG-PET for differentiating benign tumors from malignant tumors during the initial staging of breast cancer and for evaluating axillary lymph node involvement. It notes, however, that there are too few data on the utility of PET in evaluating the response to breast cancer treatment, but that, despite the paucity of available data, FDG-PET or ^{11}C-MET PET could be useful in this application by showing a response to therapy earlier than conventional imaging. However, the samples were small. Further research is necessary to confirm the efficacy of PET in imaging breast cancer.

The VA-TAP mentions a number of potential uses of PET for imaging breast cancer: the nonsurgical evaluation of breast disease; staging recurrent disease; quantifying the tumor glycolytic rate as a prognostic factor; monitoring response to therapy; selecting patients for axillary dissection and preoperative therapy; screening in certain subgroups of women (e.g., those with breast implants, prior radiation therapy, multiple breast masses and negative biopsy results, or severely fibrocystic breasts). Despite PET's high potential in breast cancer, prospective, blinded, comparative studies are necessary to better define its role in this application in relation to other imaging modalities [Flynn and Adams, 1996; Adams and Flynn, 1998].

The INAHTA states that no review has accurately determined the role of PET in patients with breast cancer [Adams et al., 1999].

Coverage policymakers

For this application, the HCFA referred the coverage decision to the MCAC Diagnostic Imaging Panel and will generate internally a new request for a national coverage decision.

The MSAC (Australia) does not mention breast cancer.

A7.1.7 Prostate cancer

Table 26: Positions – Prostate Cancer

Appendix 7: Positions according to the clinical use of PET

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BLUE CROSS BLUE SHIELD 2000	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
	✿	NM	NM	NM	NM	NM	✿	✿	NM	NM	NM

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

The members of the FMSQ's PTC believe that FDG has a limited ability to detect primary carcinoma of the prostate and to differentiate between a malignant tumor and benign prostatic hyperplasia. They recognize the utility of FDG-PET in investigating recurrent carcinoma of the prostate. Other studies are necessary [Laplante, 2000].

The ARQ, AMSMNQ and CMI do not mention prostate cancer.

Assessment agencies

The MHTAC states that, although ^{18}F-FDG has been used in certain cases of prostate cancer, radiotracers other than ^{18}F-FDG may be more effective. The data are presently insufficient to draw any conclusions concerning the role of PET in prostate cancer. The INAHTA and VA-TAP do not mention this type of cancer.

Coverage policymakers

PET is not covered for prostate cancer in the United States or Australia.

A7.2 NEUROLOGY

A7.2.1 Dementia and Alzheimer's disease

Table 27: Positions – Dementia and Alzheimer's Disease

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES		
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BLUE CROSS BLUE SHIELD 2000	VA-TAP 1998	AHTAA	INAHTA 1999
ALZHEIMER'S DISEASE	✿	NM	✿	✿	✿	NM	✿	✿/✿	✿/✿	✿/✿
DEMENTIA	✿	NM	✿	✿	✿	NM	✿	NM	NM	NM

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users

The AMSMNQ states that FDG-PET can be used to evaluate patients with dementia or memory loss (Alzheimer's disease, Parkinson's disease, etc.), although there are few treatments for these diseases. PET can be used to confirm the degenerative process even before the onset of conclusive clinical symptoms. Early diagnosis enables patients and their families to plan the patient's environment and to provide the necessary home maintenance resources.

The members of the FMSQ's PTC committee note that, because of the differences between the impairments in Alzheimer's disease and vascular dementia, PET can be used to target areas of metabolic dysfunction, confirm the diagnosis, rule out a differential diagnosis of depression and evaluate therapy [Carmant, 2000].

The CMI (Ontario) states that there are no noninvasive diagnostic tests to confirm a diagnosis of Alzheimer's disease before an autopsy. The FDG-PET has been proposed as a diagnostic tool, but the CMI concludes that its utility has not been clearly determined. It also points out that, once effective treatments have been developed for this disease and for other diseases associated with dementia and memory loss, there will ensue a significant increase in the number of requests for brain PET scans.

The ARQ does not mention the use of PET in dementia or memory loss.

Assessment agencies

The INAHTA states that the main role of PET in Alzheimer's disease would be the differential diagnosis vis-à-vis other diseases that are treatable or reversible. Furthermore, although there is still no treatment for Alzheimer's disease, psychosocial techniques and pharmacologic treatments for slowing the progression of the disease are now available and can improve these patients' quality of life. The assessments compiled by the INAHTA confirm that the accuracy of PET in the differential diagnosis of Alzheimer's disease is comparable or superior to that with other imaging techniques (e.g., CT, MRI, digital SPECT and EEG) but that its quality is nonetheless low. The value attached to a diagnosis of Alzheimer's disease in terms of patient management or the improvement in clinical outcomes has not been studied. This is why PET's potential in the diagnosis of this disease should be considered in light of the facts that there is no treatment for the disease and that other amply documented diagnostic techniques are similar to PET from the standpoint of efficacy [Adams et al., 1999].

According to the AHTAA, although PET may prove useful in contributing to the diagnosis of Alzheimer's disease, the current lack of clear therapeutic options for improving the prognosis and the lack of suitable scientific evidence concerning the value of PET prevent its use in clinical practice. A highly accurate diagnostic test should be demonstrated first in the context of epidemiological research and in the evaluation of potential therapies. Furthermore, the use of PET should be clearly situated in relation to all other available diagnostic tests (clinical, epidemiological and genetic) for this disease.

The VA-TAP states that the existing evidence argues against the clinical use of PET for diagnosing Alzheimer's disease until more effective treatments and risk modification interventions are validated and until reliable predictive values are obtained from an ongoing European multicentre PET study [Flynn and Adams, 1996; Adams and Flynn, 1998].

Coverage policymakers
For this application, the HCFA referred the coverage decision to the MCAC Diagnostic Imaging Panel and will generate internally a new request for a national coverage decision.

The MSAC does not mention Alzheimer's disease.

A7.2.2 Refractory epilepsy

Table 28: Positions – Refractory Epilepsy

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES		
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BCBSA	VA-TAP 1998	AHTAA	INAHTA 1999
DETERMINING THE LOCATION OF EPILEPTOGENIC FOCI	✿	✿	✿	✿	✿	✿	✿	NM	✿	✿/✿

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Current and potential users
The members of the FMSQ's PTC consider that the use of interictal PET for localizing epileptogenic foci is now confirmed and widely practiced at specialized centres [Couillard, 2000]. Its advantage over other diagnostic modalities is that it can be performed between seizures, unlike digital ictal SPECT, for example, which must be performed several times. Furthermore, PET can reveal areas of cortical dysplasia that cannot be visualized with magnetic resonance imaging, delineate the area of epileptic dysfunction in conjunction with an EEG and digital SPECT, substitute for preoperative functional localization tests, especially in pediatric patients, and be used for the preoperative evaluation. According to the PTC, PET can also obviate the need for costly investigations with implanted or deep electrodes [Carmant, 2000].

The AMSMNQ supports the use of PET in the evaluation of epilepsy during the interictal phase for isolating an epileptogenic focus with a view to surgery in patients who are poorly controlled with medications [AMSMNQ, 2000]. It notes that the combined use of PET and MRI permits accurate localization of epileptogenic foci and can obviate the need for invasive monitoring with deep electrodes, a labour-intensive and expensive procedure whose results are difficult to interpret [AMSMNQ, 2000].

The ARQ and the CMI (Ontario) briefly mention PET's utility in investigating certain epileptic patients whose epileptogenic foci cannot be localized with computed tomography or magnetic resonance imaging. Apart from PET, the placement of electrodes, a procedure that requires brain surgery, is the only means of localizing epileptogenic foci. However, this use is limited to ultraspecialized centres for the treatment of epilepsy [ARQ, 2000; CMI: Beanlands et al., 1999].

Assessment agencies

The INAHTA concludes that the quality of the evidence on which the efficacy of interictal PET has been determined for epilepsy is insufficient. The assessments reviewed by the INAHTA suggest that the diagnostic accuracy of interictal FDG-PET is comparable or superior to that of other methods of localizing epileptogenic foci, but the INAHTA maintains that the available evidence is still insufficient to recommend substituting PET for other, invasive diagnostic modalities and nonexistent for recommending its use in patients with nontemporal lobe epilepsy. It recognizes that PET could be beneficial in a minority of patients whose epilepsy is difficult to control, but its impact on the management of epileptic patients, the final outcome of the disease and the costs is still not known [Adams et al., 1999].

The VA-TAP does not mention epilepsy.

Coverage policymakers

The MSAC (Australia) recognizes the use of PET in the preoperative evaluation of individuals with medically refractory epilepsy in the context of a comprehensive epilepsy program, where the information obtained from a standard assessment, including seizure semiology, EEG and MRI, is inconclusive. However, it notes the lack of information on false-negative results with PET (specifically, in patients with negative PET findings who are eligible for surgery and patients with false-positive findings who are actually inoperable).

The HCFA recommends coverage of PET for the preoperative evaluation of patients with medically refractory epilepsy.

The BCBSA-TEC observes that FDG-PET imaging for the purpose of localizing epileptogenic foci and assessing their resectability in patients with refractory epilepsy meets its acceptance criteria [Adams et al., 1999].

A7.2.3 Brain tumors (glioma)

Table 29: Positions – Neuro-oncology (brain tumors, mainly glioma)

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE			ASSESSMENT AGENCIES			
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	CMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	BCBSA	MHTAC 2000	AHTAA	VA-TAP 1998	INAHTA 1999
PREOPERATIVE EVALUATION	✿	NM	NM	NM	NM	✿	✿		NM	NM	✿
DEFINING TUMOR HISTOLOGY	NM	NM	NM	NM	NM	NM	✿	✿	NM	NM	✿
GRADING TUMORS	NM	NM	NM	NM	NM	✿	✿	NM	NM	NM	NM
PATIENT MANAGEMENT	✿	NM	NM	NM	NM	✿	✿	✿	NM	NM	✿
PROGNOSIS	NM	NM	NM	NM	NM	✿	✿	NM	NM	NM	NM
DETECTING CNS* AND NON-CNS METASTASES	NM	NM	NM	NM	NM	NM	✿	✿	NM	NM	✿
FOLLOW-UP (DIFFERENTIATING BETWEEN POST-OPERATIVE SCAR AND POSTTREATMENT RECURRENCE)	✿	✿ (in combination with MRI)	✿	✿ (in combination with MRI)	NM	✿	✿	✿	✿	NM	✿
EVALUATING THE MALIGNANT TRANSFORMATION OF A LOW-GRADE GLIOMA	NM	NM	✿ (as a substitute for surgery)	NM	NM	✿	✿	✿	NM	NM	✿

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.
- Central nervous system.

Current and potential users
The members of the FMSQ's PTC support the use of PET prior to surgery for central nervous system (CNS) tumors, specifically, differentiating between radionecrosis and tumor recurrence in cases of glial tumors; determining the location of functional areas in the cortex prior to surgery; and a systematic investigation in cases of a brain lesion of undetermined nature [Couillard, 2000].

The ARQ and the CMI (Ontario) maintain that FDG-PET in combination with magnetic resonance imaging is the examination of choice, when following patients with a brain tumor, for differentiating scar from posttreatment recurrence. The CMI considers that PET should be used in conjunction with computed tomography and magnetic resonance imaging in such cases.

The AMSMNQ states that PET is effective in differentiating between a residual or recurrent brain tumor and radionecrosis and for evaluating the malignant transformation of a low-grade glioma.

Assessment agencies
The MHTAC states that ^{18}F-FDG-PET has potential for brain tumor imaging but that its clinical application has not yet been established, since this technique is unable to define brain tumor histology. In addition, further research would be necessary in order to assess the role of PET in detecting CNS and non-CNS brain metastasis, differentiating malignant from

nonmalignant lesions, detecting recurrent disease in patients who have undergone intensive radiation therapy, and evaluating brain tumors in pediatric patients. Due to the paucity of data on radiotracers other then ^{18}F-FDG, further study is required to validate the use of PET with other radiotracers to evaluate brain tumors.

The INAHTA points out the contradictions between the different assessments regarding this application. The BCBSA concluded that the evidence was insufficient to determine the effect of PET on outcomes in uses concerning brain tumors; the CAHTA [1993] concluded that PET's diagnostic performance in differentiating radionecrosis from recurrence or a persistent tumor is better than that of conventional imaging techniques; and the AHTAA noted that, despite its apparent superiority to magnetic resonance imaging in this application, PET is inferior to digital SPECT. Given these contradictions, the INAHTA concludes that the clinical impact of PET has not been documented and that the overall quality of the available evidence is low. Further research is necessary [Adams et al., 1999].

The VA-TAP does not mention brain tumors.

Coverage policymakers

The HCFA does not mention brain tumors.

The MSAC (Australia) maintains that the evidence is insufficient to conclude that PET is superior to digital SPECT in differentiating between radionecrosis and recurrent glioma. It states that the information on PET's potential to alter the management of patients with glioma is valuable, but that there are practically no data on the impact of this modification on their morbidity, mortality or quality of life, although it is reasonable to expect improvements in these parameters. Long-term outcome trials should provide this information. As for tumor grading, evaluating the malignant transformation of glioma and the preoperative evaluation, the MSAC recommends that exhaustive, systematic reviews be undertaken.

A7.3 CARDIOLOGY

Table 30: Positions - Cardiology

	CURRENT AND POTENTIAL USERS				POLICYMAKERS → COVERAGE		ASSESSMENT AGENCY
	FMSQ (PTC) 2000	ARQ 2000	AMSMNQ 2000	OCMI 1999	HCFA (US) 2000	MSAC (AUSTR.) 2000	INAHTA 1999
MYOCARDIAL VIABILITY *INITIAL EVALUATION OF PATIENT AND SELECTION FOR BYPASS*	✿	✿	✿ (together with a resting perfusion study)	✿	✿ (in place of SPECT or after a SPECT scan that is unrevealing)	✿	✿
ASSESSING PATIENTS FOR HEART TRANSPLANT	✿	NM	NM	NM	NM	NM	NM
POSTOPERATIVE EVALUATION	NM	✿	NM	NM	NM	NM	NM
CORONARY PERFUSION *DIAGNOSIS AND PROGNOSIS OF CORONARY ARTERY DISEASE*	✿	✿	✿	✿	✿	✿ (cost-effectiveness not determined)	✿
MONITORING RESPONSE TO THERAPY	✿	✿	NM	✿	NM	NM	NM
DETECTING DIMINISHED CORONARY RESERVE IN PATIENTS WITH ISCHEMIA THAT IS NOT ASSOCIATED WITH CORONARY ARTERY DISEASE	✿	NM	✿ (in the context of equivocal results with myocardial perfusion scintigraphy)	✿	NM	NM	NM

✿Clinical use recognized; ✿Clinical use not recognized; ✿ Potential use (further research necessary); NM: Not mentioned.

Users in Québec, cardiology (expert opinions): Dr. Peter Bogaty, 2000.

The tabled report, as it appears from the scientific literature that was examined, concludes that PET has proven to be useful in evaluating myocardial viability; selecting, for revascularization, patients with compromised left ventricular function; and selecting patients for a heart transplant [Bogaty, 2000 *in* Comité sur la technologie du positron, 2000].

The value of PET for studying myocardial perfusion has been demonstrated in the following uses: the diagnosis and prognosis of coronary artery disease, the diagnosis of coronary artery disease in subsets of patients who are prone to false-positive results with conventional nuclear medicine techniques (obese patients, women with atypical symptomatology, etc.), evaluating the progression or regression of coronary artery disease under treatment (e.g., with lipid-lowering agents), and detecting diminished coronary reserve in patients with an ischemic substrate that is not associated with coronary artery disease (hypertrophic cardiomyopathy, cardiac syndrome X, etc.), since no other diagnostic modality is currently able to provide information with as much accuracy.

Thus, there are many recognized and potential uses of PET. In addition, PET will, in the next few years, be used frequently in cardiology research. The report calls attention to the very short half-lives of the radiotracers used in cardiology and to the need to install cyclotrons at cardiology centres so as not to compromise the use of PET in this area.

Users in Québec, radiology (expert opinions): AMSMNQ and ARQ, September 2000.
PET should be the best technique for detecting ischemic but viable myocardium and evaluating myocardial perfusion, thus permitting better patient selection for revascularization. PET is considered an imaging modality with an established role. Steps should therefore be taken to ensure its accessibility by the Québec population, especially in cardiology [AMSMNQ, 2000; Bourgouin, 2000].

User outside Québec (expert opinion): the CMI (Ontario), 1999.
FDG-PET imaging has proven utility in evaluating myocardial viability for:

- selecting patients with reduced cardiac function for revascularization; and
- selecting candidates for a heart transplant.

Myocardial perfusion studies with PET have proven utility in the following applications:

- the diagnosis and prognosis of coronary artery disease.
- the diagnosis of coronary artery disease in the subset of patients prone to false-positive results with conventional nuclear imaging.
- evaluating the progression or regression of disease following pharmacologic treatment.
- detecting a decrease in coronary reserve in patients with ischemic disease that is not due to coronary atherosclerosis.

Based on the incidence of coronary artery disease and left ventricular dysfunction in Ontario and on the data for the recognized applications of PET, this test would probably be performed in 10,000 patients per year in Ontario, with each undergoing one or more scans. The CMI recommends that when deciding on the location of PET centres, patients with heart disease be considered one of the two most important priorities, the other being cancer patients [Beanlands et al., 1999].

Assessment agency: INAHTA, 1999
This was a collaborative effort concerning the current PET use and PET coverage policies in member countries of the INAHTA, and it included a synthesis of the technology assessments of PET by INAHTA members and three private American organizations (Blue Cross and Blue Shield Association Technology Evaluation Center, Emergency Care and Research Institute, and HAYES, Inc.). The synthesis involved 31 assessments from 13 organizations [INAHTA: Adams et al., 1999]. Most of these assessments were systematic, qualitative reviews.

The INAHTA's conclusions concerning cardiology are as follows:

PET provides better-quality images than conventional imaging. The metabolic information yielded by PET can improve patient selection for revascularization and increase the likelihood of successful surgery. The use of PET could reduce costs by avoiding unnecessary angiography or revascularization in certain patients.

- For myocardial perfusion studies, PET performs better, but how much so in relation to digital thallium SPECT is not clear. The extent of its contribution to patient management is not clear either. PET is more expensive than other noninvasive techniques and has still not replaced coronary angiography for evaluating coronary artery disease. For patients at intermediate risk (25 to 50% probability of having a 50% or greater stenosis in the left main artery or a greater than 70% stenosis in another artery), PET is not a cost-effective alternative to directly performing coronary angiography or other noninvasive tests, such as stress ultrasound or SPECT. There are not enough retrospective data to determine the cost-effectiveness of PET in diagnosing coronary artery disease.

- For assessing myocardial viability and/or predicting the risk of cardiac events, most assessments have shown that PET has comparable sensitivity and superior specificity to other techniques, although there have been few studies and although the methodology used often lack robustness. As for improving the probability of better postrevascularization outcomes and the realizable economic gains, there are insufficient data to confirm that PET has a favourable cost-effectiveness ratio.

- As for monitoring the effectiveness of treatment in coronary patients with hypertension or cardiomyopathy, the evidence is insufficient. This application is still being researched.

Assessment agency: Alberta Heritage Foundation for Medical Research (AHFMR), 1999.
The AHFMR is a member assessment agency of the INAHTA that provides information to policymakers in the field of health at the local, regional, national and international levels.

The conclusions of the AHFMR's report [Cowley et al., 1999] are as follows:

- The review of the available literature shows that the role of the different methods for assessing myocardial viability in daily clinical practice is not clear.

- PET and dobutamine stress echocardiography provide the same level of diagnostic efficacy, but the evidence is limited.

- There is a small amount of methodologically weak evidence that PET has some predictive value concerning the clinical outcome of patients who undergo this test.

PET is a promising imaging technique, but the evidence of its clinical benefits is still insufficient. The comparison with other techniques for assessing viability is limited. In Alberta, the use of these methods for assessing myocardial viability should be used in prospective studies with a long-term follow-up.

Coverage policymaker: MSAC, March 2000 [Ghersi et al., 2000].
The MSAC specifically examined the role of PET in evaluating coronary artery disease in patients with left ventricular dysfunction who have had a previous digital SPECT scan showing uncertain myocardial viability or that the myocardium is not viable.

The report [MSAC: Ghersi et al., 2000] presents the criteria for selecting articles from the literature, which led to the review of 103 references. Additionally, 126 abstracts and 33 articles were examined.

It seems that the sensitivity and specificity of PET are superior to those of single-positron emission computed tomography. Although PET provides better diagnostic accuracy, this improvement is difficult to quantify because of flaws in the study designs.

The MSAC concludes that presently, there is not enough evidence to draw any firm conclusions about the clinical efficacy and cost-effectiveness of PET in this application. In most cases, PET is added to other diagnostic modalities. Further assessments of this technology are needed. The committee recommends that FDG-PET be covered on an interim basis for the evaluation of patients with ischemic heart disease with left ventricular dysfunction who are being considered for revascularization and in whom evaluations of myocardial viability using conventional techniques have yielded negative results. However, the committee stipulates that clinical and/or economic data from MSAC-approved prospectively designed studies must be provided to a central body so as to permit more long-term decisions to be made about the role of FDG-PET in clinical practice.

Coverage policymaker: HCFA, 2000 [Tunis et al., 2000]
The analysis of the problem in cardiology is based on the work presented in the Australian report entitled "Commonwealth Review of Positron Emission Tomography", drafted by Ghersi et al. [1999], who reviewed 33 articles on the efficacy of PET as a diagnostic test. None of the articles met the predefined criteria for methodological quality. As regards the impact of FDG-PET findings on patient health, in cases where the SPECT scan is negative and the PET scan is positive, there are insufficient literature data to state that a change in patient management would result in improved health outcomes. In cases where the SPECT scan is positive but questions remain as to the appropriateness of revascularization, PET could be a promising test, based on the literature examined.

Medicare covers rubidium-82 PET for evaluating myocardial perfusion at rest or with pharmacological stress in the context of managing patients with known or strongly suspected coronary artery disease, when PET is used as a replacement for SPECT or when the SPECT findings are equivocal.

Medicare (U.S.) does not cover PET scans for screening for coronary artery disease, regardless of the number or importance of the patient's risk factors.

In December 2000, Medicare also began covering FDG-PET for evaluating myocardial viability following a positive SPECT scan, but when there is doubt as to myocardial viability if revascularization is being considered.

Coverage for this test in other applications was referred for study to an advisory committee consisting of nuclear imaging experts.

Appendix 8

Selected Studies on PET

APPENDIX 8: SELECTED STUDIES ON PET

A8.1 LUNG CANCER

Table 31: Selected studies on PET (oncology)

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
Erasmus et al., 2000	Lung cancer	English AJR	25 patients (18 men and 7 women; age: 37 to 86 years).	No	Visual analysis of axial and coronal plane images.	Primary NSCLC and pleural effusion. Retrospective design: 1993-1999.	All eligible patients included.	Not mentioned. PET scans assessed by experienced observers, CT scans by thoracic radiologists.	Thoracentesis or pleural biopsy. Blinded to PET results.	Scanner with an axial field view of 15.2 cm. Imaging of chest and upper abdomen performed 1 hr after the admin. of 10 mCi of FDG. Images reconstructed and data corrected for scatter and random events.		In detecting pleura metastases: PET 95% (CI: 77-100%) (21/22). Accuracy of 92% (CI: 74-99) (23/25)
Gupta et al., 2000	Lung cancer	English CHEST	118 cases, but 54 underwent surgical test and were included in the analysis (73 men; age: 35-84).	No	Visual analysis in axial, coronal and sagittal views. Quantitative analysis (SUV: standardized uptake value). An FDG uptake of 4-5 was classified as malignant, 1-3 as benign.	Patients with proven or suspected NSCLC who were candidates for surgery. Consecutive cases.	All eligible patients included, but only 54 of the 118 patients were included in the analysis.	Yes. PET scans read by nuclear physicians, CT scans by radiologists.	Mediastinoscopy or bronchoscopy followed by thoracotomy.	Whole-body FFD-PET. Axial view of 14.6 cm in 3-4 bed positions. Scanning performed 60 min after the admin. of 10 mCi of FDG. Patients fasted for at least 4 hrs. Data reconstructed and partial volume corrected.		Staging o mediastinal lymph nodes: PET <1 cm: 82% (15/17) 1-3 cm: 100% (32/32) > 3 cm: 100% (4/4) Overall PET: 96% (51/53) Accuracy 94% (158/168) CT: 68% (36/53) Accuracy 66%.
Vanuytsel et al., 2000	Lung cancer	English Radiation Therapy and Oncology	105 patients (age and sex distribution not given).	Yes. Overlapping of cases with two	Visual analysis in transaxial, sagittal and coronal planes. Quantitative (GTV)	Patients with operable NSCLC (detailed description). Prospec-	All patients included, but not all were in-	Yes. PET scans read by two nuclear physicians, CT	Mediastinoscopy and thoracotomy.	CTI/Siemens scanner with an axial field view of 10.1 cm. Fasting		Lymph node staging: PET 72% (64/89) CT 47%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
				previously published studies.	analysis.	tive design.	included in the analysis.	scans by a chest radiologist.		for at least 6 hrs. Scanning in two bed positions, with attenuation correction (max. 555 MBq of FDG) 60-70 min. after admin. of FDG.		(42/89) PET + CT 78% (69/89) Accuracy PET: 95% (943/988) CT: 89% (887/988) (p< 0.001
Higashi et al., 2000	Lung cancer	English Nucl Med Commun	35 patients (age: 46-84, including 14 men).	No	Visual analysis and semi-quantitative (SUV) analysis of FDG uptake.	Pulmonary adenocarcinoma (Jan 1995 to Nov 1998). Retrospective design.	All eligible patients were included in the study and analysis.	Not mentioned. PET scans were read by two of the authors.	Thoracotomy	PET camera PET with an axial field view of 10 cm. Average FDG dose: 157 MBq. Scanning performed 40 min. after admin. of FDG in 2 bed positions. Images reconstructed using measured attenuation.		No data
Marom et al., 1999	Lung cancer	English Radiology	100 patients, age: 25-83 (with 58 men).	No	Visual analysis and quantitative (SUV) analysis of FDG uptake.	Patients with newly diagnosed cancer or suspected from radiological study (Nov 1995 to July 1997). Retrospective design, consecutive patients.	39 patients excluded for various reasons, such as poor-quality PET scans.	Yes. PET assessed by nuclear medicine physicians, CT by experienced chest radiologists.	Needle biopsy, mediastinoscopy, thoracoscopic biopsy. Test not influenced by PET results.	Fasting for at least 4 hrs before the admin. of 5.365 kBq/kg of FDG. Scanning performed 30 min. after injection. 2 bed positions, with attenuation correction. Images re-		Lymph nodes (N3): PET: 92% (22/24) CT: 25% (6/24) (P= 0.005 Pulmonar metastases: PET: 94% (17/18) Accuracy: 98% (98/100)

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										constructed. SUV calculated by dividing the mean activity in the lesion by the dose of FDG administered per kg of body weight after attenuation.		CT: 78% (14/18). Accuracy: 91% (91/100)
Bénard et al., 1999b	Lung cancer	English J Nucl Med	28 patients followed, but analysis concerned only 17 of them (14 men; age: 48-78).	Yes. Same patient population as in a previous study.	Visual analysis and quantitative (SUV) analysis of FDG uptake in the tumor.	Patients with proven or suspected mesothelioma (Sep 1995 to May 1997). Reference given for details and description of population.	All 28 patients included, but the quantitative analysis involved only 17 of them.	Not mentioned.	Histology	PENN-PET 240H scanner. Fasting for at least 4 hrs. 4.218 MBq/kg of FDG, with scanning performed 60-90 min. after injection. Attenuation correction and image reconstruction.		No data given.
Vansteenkiste *et al.*, 1998	Lung cancer	English J Clin Oncol	68 patients, age: 40-83. Sex distribution not given.	No? (cases in this study overlapped with those in another study).	Visual analysis of transaxial, sagittal and coronal images and quantitative (SUV) analysis of FDG uptake.	Patients with proven or suspected NSCLC operable after staging with conventional imaging, including CT (Sep 1995 to Jan 1997). Prospective design.	Not all eligible patients were enrolled in the study because of schedule conflicts and lack of consent.	Yes. PET assessed by 2 nuclear medicine physicians, CT by 2 chest radiologists.	Invasive mediastinal staging.	PET camera with an axial field view of 10.1 cm. 10 mCi of FDG admin. after fasting for at least 6 hrs. Scanning 60 min. after admin. of FDG. Reconstruction and at-		Locally advanced disease (N2/N3): PET + CT 93% (26/28) Accuracy: 94% (64/68) CT: 75% (21/28) Accuracy: 68% (46/68) Individual metastatic lymph node stations: PET + CT 89%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										tenuation of images.		(42/47) Accuracy: 98% (678/690), CT: 47% (22/47) Accuracy: 92% (638/690)
Pieterman *et al.*, 2000	Lung cancer	English N Engl J Med	102 patients (including 88 men); age: 25-77.	No	Visual analysis of hot spot.	Patients with potentially operable NSCLC who were being evaluated with conventional imaging (Sep 1996 to Dec 1998). Prospective design, consecutive patients.	All eligible patients were included.	PET and CT assessed in a blinded fashion by 2 observers.	Histopathology – nodal examination with cervical mediastinoscopy, parasternal mediastinotomy and exploratory thoracotomy.	Scanner with an axial field view of 10.8 cm. Fasting for at least 6 hrs before the admin. of 370 MBq of FDG. Scanning began 90 min after injection. Images corrected for attenuation and reconstructed.		Mediastinal metastase: Based o 32 patient PET: 91% (CI: 81-100) Accuracy: 87% (CI: 80-94) CT: 75% (CI:60-90 Accuracy: 69% (CI: 60-78) PET + CT 94% (CI: 86-100) Accuracy: 88% (CI: 82-94) Distant metastase: Based o 17 patient PET: 82% (CI: 64-100) Overall PET: 95% (CI: 88-100)
Barkheet *et al.*, 2000	Lung cancer	English Clin Nucl Med	10 cases. Age and sex distribution not given.	No	Visual analysis	Patients with cancer (March 1996 to July 1997). Retrospective review.	All eligible patients were included in the study and analysis.	No mention of those who evaluated the images or whether or not they were blinded.	Histopathological nodal sampling.	Scanner with an axial field view of 16.2 cm. 7 to 10 mCi of FDG admin. after 12-hr fast. Whole-body scanning 45-60 min after injection. Images		No data

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										reconstructed using Hann filter. Not all images corrected for attenuation.		
Roberts et al., 2000	Lung cancer	English Ann Thorac Surg	100 patients; age and sex distribution not given.	No	Visual analysis in axial, coronal and sagittal planes. Semiquantitative (SUV) analysis of FDG uptake.	Patients with early NSCLC referred for PET scan and who had pathological confirmation (Jan 1995 to April 1999). Retrospective review.	All eligible patients were included in the study and analysis.	PET images read by nuclear physicians but no mention of blinding.	Histopathology – mediastinoscopy, mediastinotomy or thoracotomy	Scanner with an axial field view of 16.2 cm. Fasting for at least 4 hrs before the admin. of 0.143 mCi/kg of FDG. 6 bed positions. Whole-body scanning 30-45 min after injection. Images reconstructed with/without attenuation correction.		Mediastinal metastases: PET 87.5% (21/24) Accuracy 90% (90/100)
Hara et al., 2000	Lung cancer	English J Nucl Med	29 patients; age: 40-83 (including 19 men).	No	Semiquantitative (SUV) analysis of FDG uptake in the tumor.	Patients with biopsy-proven NSCLC and mediastinal lymph node metastases regarded as NO, N1 or N2 by CT. Retrospective design.	All eligible patients were included.	Yes. PET images read by 2 blinded radiologists.	Histopathological nodal sampling.	Scanner with 6-mm spatial resolution. 12-hr overnight fasting and injection of 370 MBq of FDG. Scanning from neck to liver 40 min after injection. 6 bed positions. Attenuation correction by combining		Detection of mediastinal lymph node metastases: PET-FDG 75% (68/90) Accuracy 96% (251/261) CT 19% (17/90) Accuracy 94% (245/261) ^{11}C-choline PET 100% (90/90) Accuracy 97%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										transmission and emission data in a computer.		(253/261)
Weber et al., 1999	Lung cancer	English Eur J Nucl Med	27 patients; mean age: 62 ± 9 (26 men).	No	Visual analysis and semiquantitative (SUV) analysis of FDG uptake in the primary tumor and involved lymph nodes. Images interpreted on computer screen using linear gray scale.	Patients with lung cancer or intermediate pulmonary nodules. Retrospective design.	All eligible patients were included.	Yes. PET scans read by 2 experienced observers, CT by 2 radiologists.	Histopathology (biopsy or thoracotomy).	Full-ring scanner with an axial field view of 16.2 cm. Admin of 185-270 MBq of FDG after 4 hrs of fasting. PET images reconstructed with (ac) and without (nac) attenuation correction using penalized least-square algorithm.		Detection of lymph node metastases: PET (ac) 100% (11/11) PET (nac) 91% (10/11) CT 91% (10/11) CGC 73% (8/11)
Vesselle et al., 2000	Lung cancer	English Clinical Cancer Research	39 patients. Age and sex distribution not given.	No	Quantitative analysis of tumor FDG uptake, quantitated with the maximum pixel standardized uptake value (SUV).	Patients with operable NSCLC who underwent resection or surgical biopsy (Feb 1998 to June 1999). Prospective design.	All eligible patients were included in the study and analysis.	No mention.	Surgical staging (bronchoscopy and mediastinoscopy with or without thoracotomy). Immunochemistry for Ki-67 (proliferation index marker). Specimens were reviewed for cellular differentiation (poor, moderate, good) and tumor type.	Whole-body FDG. 12-hr fast. Admin. of 7-11 mCi of FDG. Scanning in the thoracic plane 45 min after injection. Images collected in 2 dimensions. Data reconstructed and corrected using standard filtered back-projection.		No data given.
Berlan-	Lung	English	50 patients:	No	Visual	Patients	All	Yes. PET	Mediastino-	Scanner		Nodal

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
gieri et al., 1999	cancer	Cardiothoracic Surgery	37 men; age: 41-78.		analysis grade on a 5-point scale.	suspected of having NSCLC who remained surgical candidates after conventional imaging and staging. Consecutive cases.	eligible patients were included.	assessed by a nuclear medicine physician, CT by a blinded radiologist.	scopy or thoracotomy.	with an axial field view of 10 cm. Admin. of 400 MBq of FDG. Thorax and upper abdomen emission scan acquired after 45 minutes. Attenuation correction made. Reconstruction with Hanning filter.		staging: PET 80% (16/20) CT 65% (13/20)
Saunders et al., 1999	Lung cancer	English/ Ann Thorac Surg	97 patients: 64 men; age: 36-77.	No	Visual analysis in the transaxial, coronal and sagittal slices, and quantitative (SUV) analysis of tissue uptake.	Patients with suspected or proven lung cancer referred for possible surgery (Nov 1992 to July 1995, and followed until July. 1996).	All eligible patients were included in the study, but only 84 of the 97 patients were included in the analysis.	Yes. PET assessed by 2 nuclear medicine physicians.	Mediastinoscopy or thoracotomy.	ECAT 951/31R scanner. 6-hr fast. Admin. of 350 MBq of FDG. Images of the chest acquired after 81 min. Attenuation corrected, and images reconstructed.		Mediastinal staging: (N2 and N3): PET 70.6% (12/17)* CT 20% (3/15)*
Magnani et al., 1999	Lung cancer	English J Cardiovasc Surgery	28 patients: 26 men; age: 50-75.	No	Visual analysis of FDG uptake compared with blood pool activity.	Patients with proven NSCLC waiting for surgery. Retrospective design.	All eligible patients were included.	PET and CT assessed by independent observers.	Bronchoscopy or needle biopsy as well as mediastinoscopy or thoracotomy.	Whole-body scanner with an axial view of 15.4 cm 10-min emission scan 50 min after inj. of 370 MBq of FDG. Transaxial		Mediastinal lymph node staging: PET 67 % (6/9) CT 66% (6/9) PET + CT 78% (7/9)

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										images reconstructed with Hann filter and corrected for attenuation.		
Dhital et al., 2000	Lung cancer	English Eur J Cardiothoracic Surg	97 cases, but only 77 were included in the analysis (53 men; age: 36-77).	Yes	Visual analysis	Patients with suspected or proven lung cancer clinically considered operable (Nov 1992 to July 1995). Retrospective design.	Of the initial 97 patients, only 77 were included in the analysis.	2 blinded nuclear medicine physicians.	Histological diagnosis by bronchoscopy, transthoracic needle biopsy or thoracotomy.	ECAT 951/31R scanner. Fasting for 6 hrs. Admin of 350 MBq of FDG. Thoracic emission began 81 min later. Attenuation corrected, and images reconstructed.		No data

A8.2 COLORECTAL CANCER

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
Valk, et al. (1999)	Colorectal cancer	English Arch Surg	115 consecutive patients for diagnosis or staging of recurrent colorectal cancer.	No	Visual analysis in axial, coronal and sagittal planes.	All patients with confirmed or suspected recurrent colorectal cancer (Oct 1992 to May 1996).	21 pts excluded due to lack of a criterion standard. 6 followed for less than 1 year, 6 lost to follow-up, 5 died, 4 treated without further validation.	CT and PET interpreted blindly and read together by 1 or 2 investigators.	PET was performed after the CT (between 0-56 days).	Yes. ECAT EXACT 921 scanner. Patients fasted for at least 4 hrs prior to injection of FDG, 5.29 MBq/kg (0.14 mCi/kg). 4 minutes per bed position. Scanning began 30 minutes after injection.	With disease: Liver: 57 Pelvis: 31 Abdomen: 28 Retroperitoneum: 12 Lungs: 17 Other: 12 Total: 157 Without disease: Liver: 58 Pelvis: 84 Abdomen: 87 Retroperitoneum: 103 Lungs: 98 Other: 104 Total: 534	PET Liver: 95% Pelvis: 97% Abdomen 79% Retroperitoneum 100% Lungs: 94% Other: 100% Total: 93% CT Liver: 84% Pelvis: 68% Abdomen 46% Retroperitoneum 58% Lungs: 94% Other: 33% Total:

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
												69%
Imdahl et al. (2000)	Colorectal cancer	English Langenbeck's Arch Surg	71 patients (77 investigations) with suspected recurrence, metastases or elevated CEA.	No	By 2 independent investigators. Lesions classified as malignant by focally increased uptake exceeding the normal limits in the respective areas or a standardized uptake value (SUV) > 4.	Unclear	Unclear	Interpretations were blinded to the clinical data and the results of the conventional imaging. Scans read by 2 independent investigators.	Comparison with CT, ultrasonography, MRI and chest x-ray.	> 6 wks after the last chemotherapy or more than 3 months after the completion of radiation therapy. Patients fasted for 12 hrs. Bladder catheter was inserted unless patient did not give consent. Siemens/CT I ECAT EXACT 921/31 scanner. Scanning done 90 minutes after injection of 350 ± 50 MBq in cubital vein.	Liver metastases in 28 patients (43 lesions). Pulmonary metastases in 17/77 investigations.	Detection of local recurrence: PET: 92% CT: 88% MRI: 83 Detection of hepatic metastases: PET: 100% CT: 87% MRI: 100%
Zhuang et al. (2000)	Liver metastases from colorectal cancer	English Nuclear Medicine Communications	80 patients	No	Not explicitly stated. Assumed visual.	Consecutive patients recruited retrospectively.	96 consecutive FDG-PET patients with confirmed colorectal cancer. 16 excluded (lack of concurrent anatomical imaging, nega-	Not stated.	Results of PET and CT were compared with those of surgical pathology and clinical follow-up.	Scanning with C-PET camera within 8 weeks of conventional imaging. Fasting for at least 4 hrs prior to injection of 2.516 MBq/kg of FDG. Image acquisition began 40 min postinjection. Attenuation correction us-	28 with hepatic metastases, 52 without hepatic metastases.	Detection of hepatic metastases: 100% CT: 71.4

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivi
							tive findings, less than 6 months of follow-up, death or lost to follow-up).			ing a caesium-137 point source. Images reconstructed using the ordered subsets (expectation maximization).		
Staib et al. (2000)	Recurrent colorectal cancer	English American Journal of Surgery	100 patients with histologically confirmed colon or rectal cancer.	No	Reconstructed images were assessed visually without quantification of FDG uptake.	Prospectively recruited from 1994 to 1998.	Patients with uncontrolled diabetes or acute inflammation were excluded	Blinded to the specific results of conventional imaging but with knowledge of clinical diagnosis and indications.	CT, liver ultrasound, and carcinoembryonic antigen (CEA).	Siemens ECAT EXACT HR+ scanner and Siemens ECAT 8/12 scanner 1 hr after the injection of 408 ± 10.5 (mean ± SE) MBq of ^{18}F-FDG. No attenuation correction.	With disease: Liver metastases: 33 Lung metastases: 17 Rectal recurrence: 20 Colon recurrence: 3 Without disease: Liver metastases: 67 Lung metastases: 83 Rectal recurrence: 35 Colon recurrence: 42	Detection of malignancy: PET: 98% 87 CT scans: 91% 98 CEA assays: 76% Detection of liver metastases: PET: 100% 68 ultrasounds: 87% Local recurrence: PET: 96%
Willkomm et al. (2000)	Recurrent colorectal cancer	English Journal of Nuclear Medicine	28 patients with suspected recurrence (15 men, 13 women).	No	2 nuclear medicine specialists unaware of the results of the conventional imaging studies. PET findings classified as "malignancy-typical" when antibody uptake was markedly higher than liver uptake.	Followed for 6 to19 months.	Inclusion and exclusion criteria not clearly stated.	Blinded to the results of conventional imaging.	Immunoscintigraphy (CEA-scan).	Siemens/CTI ECAT EXACT scanner. 12-hr (overnight) fast. Approx. 250-370 MBq of FDG injected and flushed with 20 mL of saline. Patients asked to drink 1 L of water and voided prior to examination.	With disease: Local recurrence: 9 Hepatic metastases: 9	PET: Local recurrence: 100% CEA: Local recurrence: 89%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										Scans obtained 45-60 min after injection.		

A8.3 MELANOMA

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
Paquet et al. (2000)	Metastatic melanoma	English Dermatology	24 patients (28 assessments)	No	Visual interpretation in coronal sagittal and transversal planes.	No	Unclear	Unclear	CT, MRI and ultrasound. Correlation with histological confirmation (n=11) and clinical follow-up (n=17).	150-300 mBq injected according to body weight, and scan performed 60-90 minutes after injection. UGM Penn PET 240 H scanner.	Not given.	Diagnosti accuracy of 80%.
Eigtved et al., (2000)	Metastatic melanoma	English Eur. J. Nucl. Med.	38 patients, stage II (n=27) or III (n=11).	No	Visual interpretation by 3 blinded observers, who recorded the sites of increased uptake.	Yes	Consecutive patients (Dec 1993 to Oct 1995) after resection of a melanoma.	Yes	PET results compared with the results of clinical examination and of other imaging methods (CT of chest	GE Advance PET scanner. Fasting for at least 6 hrs prior to injection (mean: 357 MBq). Scanning began	Histological diagnosis obtained in 29/38 patients (25 malignant tumors). 25 patients with malignant lesions and involvement of regional	PET: All sites: 97% Intraabdominal sites: 100% Pulmonary/intra thoracic sites: 100% Conventional methods: All sites:

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
									or abdomen if metastases were suspected in those regions). An ultrasound was performed if the clinical exam yielded suspicious findings in the regions of interest.	35-40 minutes later. After PET, a biopsy or excision of the tissues was done, if possible.	lymph nodes, 11 with malignancy in other lymph nodes, 6 with pulmonary/intrathoracic lesions, and 4 with intra-abdominal lesions.	62% Intraabdominal sites: 100%
Crippa et al. (2000)	Metastatic melanoma	English J. Nucl. Med.	38 patients with previous history of cutaneous melanoma and a current clinical diagnosis of nodal metastases.	No	Visual analysis by 2 blinded nuclear physicians. Images with at least one site of FDG uptake were considered positive for melanoma. Retrospective analysis to evaluate each lymph node basin and determine the number of sites of FDG uptake.	Yes	Current clinical diagnosis (through physical exam, ultrasound or CT) of nodal metastases.	Comparison with histology results.	PET scan done 1-3 days before surgery	GE 4096 WB scanners. Injection of a mean dose of 496 MBq of FDG. Scanning done 1-3 days prior to surgery. Patients fasted for at least 5 hrs. Mean glucose level before PET was 84 mg/dL.	With disease: 35 lymph node basins. Without disease: 19 negative for lymph node basins.	Lymph node basins: 95% Number o metastase found (compared to histology) <5 mm: 23% 6-10 mm: 83 % 11-15 mm: 100% 16-20 mm: 100% 21-25 mm: 100% > 25 mm: 100% Total: 66%
Acland et al. (2000)	Metastatic melanoma	English J. Am. Acad. Dermatol.	54 patients referred by physicians with various criteria for PET (not consistent).	Ongoing study.	Visual assessment by experienced nuclear medicine physicians (coronal, sagittal and transaxial planes).	Retrospective from PET scan database. All patients with histological diagnosis of melanoma who had	No	Comparison with histology or clinical progression of the disease. Further study to do direct comparison with sentinel	N/A	ECAT 951R whole-body scanner in extended 2-dimensional mode. 6-hr fast. Blood glucose levels	With disease: 17 patients with stage I 3 patients with stage II 14 patients with stage III. Without disease:	Overall: 87% Stage I disease: 50% Stage II disease: 33% Stage III disease: 93%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
						undergone PET.		node biopsy.		measured. Scanning began 50 minutes after the intravenous injection of 350 MBq of FDG.	27 negative for stage I. 6 negative for stage II. 2 negative for stage III.	
Krug et al. (2000)	Metastatic melanoma	English Acta Radiologica	94 patients examined retrospectively.	No	Evaluated by a radiologist, a nuclear medicine specialist and a dermatologist.	Yes. All melanoma patients referred between June 1995 and March 1999.	FDG-PET for malignant melanoma. One exclusion due to hyperglycemia.	Confirmation with histology or other imaging results.	Maximum time of 2 weeks between PET and other examinations.	ECAT EXACT scanner (Siemens/CTI). 300-400 MBq was injected as per each protocol. Maximum allowable time between PET and other examinations being compared was 2 weeks.	N/A	Could not be calculated because the numbers were too small
Wagner et al. (1999)	Melanoma	English J Clin Oncol	70 patients (89 lymph node basins).	No	By the same nuclear medicine specialist	Patients (> 18 years of age) with invasive cutaneous melanoma.	Exclusion criteria: ocular or mucosal melanoma; clinical evidence of regional lymph node metastases, or distant metastases; palpable lymphadenopathy; infection or inflammation in the regional lymph node basins; prior excision > 4 cm; lymph node dissections, skin grafts, tissue transfers, or flaps that can	Blinded investigator interpreted reconstructed images and assigned each lymph node basin at risk for being definitely positive, probably positive, uncertain, probably negative, or definitely negative.	Preoperative lymphatic mapping, SNB procedures and surgical specimens.	Preoperative whole-body PET. Siemens ECAT 951/31R PET scanner. Two imaging protocols (patients 1-24: 10 mCi of FDG injected 30 min prior to scan; patients 25-74: 60 min after injection).	Results for 89 basins.	Sentinel node biopsy for detecting occult regional lymph node metastases: 94.4% PET: 16.7%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
							alter the lymphatic drainage pattern from the primary tumor site to the regional node basins; pregnancy or breast-feeding; prior malignancy; and allergy to isosulfan blue dye or to FDG.					
Jadvar et al. (2000)	Melanoma	English Clin. Nuclear Med	38 patients studied retrospectively.	No	Visual (axial, coronal and sagittal planes) on a computer by a single, experienced observer aware of clinical history and radiology results.	All patients with primary cutaneous melanoma (≥ 1 mm in depth) evaluated between June 1995 and Aug 1997.	Not stated.	CT performed within 9 weeks after PET with no intervening therapeutic intervention.	CT results available for 21 patients.	ECAT EXACT scanner (CTI, Knoxville, TN). Imaging was done 40-60 min after the intravenous injection of 10-15 mCi (370-555 MBq) of FDG. 6 bed positions.	N/A	Not stated
Tyler et al. (2000)	Melanoma	English Cancer	95 patients (106 PET scans).	No	FDG-PET activity was assessed independently by 2 experienced observers as positive (activity > background) or negative (activity ≤ background). Final determination by consensus.	Patients with clinically evident stage III lymph node and/or in-transit melanoma.	Consecutive patients at the Duke University Medical Centre Melanoma Clinic.	PET studies were interpreted independently of CT without any knowledge of clinical or pathology results.	CT, biopsy of area of increased uptake on PET.	Fasted for 4 hrs. GE Advance medical scanner. FDG dose range of 10-20 mCi.	165 areas with melanoma. 69 negative areas.	PET: 87.3%
Dietlein et al. (1999)	Melanoma	English Nuclear Medicine Communications	68 patients with advanced melanoma.	No	PET, ultrasound and radiological data interpreted by different investigators.	91 PET scans done in 68 patients between June 1995 and Oct	Not stated.	Not stated.	CT	No standard protocol was established for the extent of the imaging or	N/A	FDG detected fewer pulmonar and hepatic metastases and fewer cerebral

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
						1997. 15 had 2 PET scans, and 4 had 3.				the timing after the injection. All came from different institutions, and all institutions used ECAT EXACT scanners (Siemens/CTI). 300-400 MBq of FDG was injected in each protocol.		foci but more lymph node and bone metastases than conventional radiology or CT.

A8.4 HEAD AND NECK CANCER

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
Di Martino et al. (2000)	Head and neck cancer	English Arch Otolaryngol Head Neck Surg	50 patients with primary or recurrent head and neck cancer.	No	Imaging procedures were performed 1-20 days prior to surgery.	Nonrandomized, comparative study from Oct 1, 1997 to Nov 30, 1998.	Exclusion criteria: diabetes mellitus and a history of acute or chronic inflammatory disease.	Not stated.	Ultrasound, CT, histopathology of biopsy specimens.	PET performed with an ECAT EXACT 922/47 scanner after a minimum 12-hr fast. 212 ± 59 MBq of FDG was administered intravenously. Scanning began 45-60 min later.	WITH CANCER PET, CT, panendoscopy: Primary: 37 Recurrent: 8 Ultrasound: Primary: 23 Recurrent: 6 WITHOUT CANCER: PET, CT, panendoscopy: Primary: 13 Recurrent: 5 Ultrasound: Primary: 4 Recurrent: 2	PET: Detection of primar tumor: 95% Recurrent carcinomas: 100% CT: Detection of primar tumor: 68% Recurrent carcinomas: 62% Panendoscopy: Detection of primar tumor: 95% Recurrent carcinomas: 100% Ultrasound: Detection of primar tumor: 74% Recurrent

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
												carcinomas: 67%
Lowe et al. (2000)	Recurrent head and neck cancer	English J. Clin. Oncol.	44 patients with stage III and IV head and neck cancer.	No	Assumed to be visual.	Patients were part of neoadjuvant organ-preservation study that included chemotherapy, radiotherapy and surgical salvage.	Unclear	CT done at 2 and 10 months. Pathology results obtained for some.	Physical exam (PE) and correlative imaging (CT).	ECAT 951/31 PET scanner (Siemens). PET done at 2 and 10 months after therapy. All patients fasted before PET studies. Glucose levels measured.	16/30 patients had recurrence after the first year. 5 were detected by PET only, 4 by PET and conventional imaging only, 5 by PE and PET, and 2 by PE, PET and conventional imaging.	PET: 100% PE: 44% Correlative imaging: 38%
Lonneux (2000)	Recurrent head and neck cancer	English The Laryngoscope	44 patients	No	Quantitative, using SUV (= activity in the 9 maximal pixels in µCi/mL) ÷ (injected dose ÷ lean body mass).	Prospective inclusion of patients with clinical manifestations of recurrence (pain, palpable mass, bleeding, dysphonia).	All patients recruited prospectively.	CT + MRI done within 2 weeks.	None	ECAT EXACT HR (Siemens/CTI). Patients fasted for 6 hours before injection of 185-370 MBq. Scanning began 45 min later.	22/38 with disease.	PET: 95% CT + MRI: 73%
Jungehulsing et al. (2000)	Unknown primary tumor with head and neck lymph node manifestation	English Otolaryngol Head and Neck Surgery	27 patients with no primary tumor found after conventional diagnostic procedures (from original 723).	No	Visual. PET images were reconstructed with filtered back-projection and displayed in coronal, sagittal and transaxial projections with the commercial software MPITool.	27 patients with no primary identified, May 1994 to July 1998.	All patients diagnosed with malignant disease at an ENT clinic were eligible (n=723).	PET findings were corroborated by fine-needle aspiration cytology, biopsy or surgery.	N/A	Siemens/CTI ECAT EXACT whole-body positron scanner. Standard dose of 370 MBq (10 mCi) was injected after a blood specimen obtained for blood glucose determination. Patients fasted for at least 6 hrs. Scanning began 60-90	N/A	Could not be calculated due to small samples.

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										min after injection. 2 bed positions.		
Bohuslavizki et al. (2000)	Unknown primary	English Journal of Nuclear Medicine	53 patients	No	Visual inspection.	Patients with metastatic cervical adenopathy or extracervical metastases were included between Jan 1997 and Jan 1999 after an extensive but inconclusive diagnostic workup.	53 patients with metastases from unknown primary tumor from Jan 1997 to Jan 1999.	No. Other results were used to interpret the PET results.	Clinical, surgical and histopathologic findings were used. In patients with suspected lung tumors, chest CT and subsequent biopsies were performed to evaluate the PET findings.	Complete patient history and physical exam (including chest x-ray) were performed prior to PET, patients fasted for at least 6 hrs, and scanning began 60 min after the injection of 370 MBq of FDG, using an ECAT EXACT 47 scanner.	With disease: 20 (10 lung, 8 head and neck, 1 breast, 1 ileocolonic area).	PET: 37.8% tru positives, 22.2% false positives
Perie et al. (2000)	Unknown primary	English Ann Otol Rhinol Laryngol	4/60 patients with untreated head and neck squamous cell carcinoma included in a prospective study of FDG.	No	N/A	March to October 1998	N/A	N/A	N/A	N/A	N/A	N/A
Lassen et al. (1999)	Unknown primary	English European Journal of Cancer	20 patients	No	Visual interpretation of PET by nuclear medicine specialists with PET experience. Semiquantitative analysis of FDG uptake was not performed.	Referred to Copenhagen University Hospital in April 1996 to Sep 1997.	Patients aged 18 to 75 with biopsy - proven metastatic disease and unknown primary tumor following physical exam, x-ray and/or CT and routine laboratory tests.	At the time of the visual interpretation, correlative information on histology and location of metastatic lesions was available.	Depended on histology.	GE Advance PET scanner. Patients fasted for at least 6 hours. 40 min after injection of 350-400 MBq of FDG in a cubital vein. The patient emptied bladder, then was placed on the PET	PET suggested primary site in 13 patients and was confirmed histologically (or by the clinical course of the disease) in 9.	Data not given.

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										scanner bed. All the PET scans were performed within 4 weeks after initial diagnostic procedures.		
Farber et al. (1999)	Recurrent head and neck cancer	English Laryngoscope	28 patients who received radiation therapy for squamous cell carcinoma of the head and neck.	No	Qualitative analysis of corrected and non-corrected images, by 2 readers.	Unclear	Unclear	Yes	CT and MRI	PENN-PET 240H PET scanner. FDG injected into a peripheral vein at a dose of 0.114 µCi/kg. Patient then placed in a lying position and instructed not to talk for 15 min before and 30-45 min after the injection. Scanned ~60 min after uptake.	14 with disease. 14 without disease.	PET: 86% CT and MRI: 71
Tiepolt et al. (2000)	Thyroid cancer	English Annals of Nuclear Medicine	31 patients	No	The PET images were reconstructed by filtered back-projection. Uncorrected images were used for comparing the results obtained with a dedicated PET scanner and on a coincidence camera and read separately by 2 blinded readers.	Not stated.	Patients with thyroid cancer who had undergone a thyroidectomy and at least 2 radioiodine treatments with a positive ^{131}I whole-body scan (n=22) and/or high thyroglobulin levels (n=27).	2 physicians were blinded to the results of the coincidence gamma camera when reading the PET scans.	Coincidence gamma camera (PET was actually the reference test). Coincidence imaging is a cost-effective alternative.	ECAT EXACT HR+ (Siemens/CTI, Knoxville, Tenn.) with BGO detectors. PET and coincidence imaging were performed on the same day. Patients fasted for at least 4	118 lesions identified in 31 patients.	Coincidence imaging compared with PET: 69% Concurrence was 96% in lesions > 1. cm and 62% in those between 1 and 1.5 cm. Lesions < 1 cm could not be identified with the coincidence

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
										hrs and had normal blood glucose levels.		camera. Identical staging obtained in 84%.

A8.5 LYMPHOMA

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
Jerusalem et al. (1999)	Hodgkin's and non-Hodgkin's Lymphoma	English Blood	54 patients included (19 HD, 35 NHL)	No	Qualitative analysis without correction (transversal, coronal and sagittal planes).	Unclear. Patients recruited prospectively from June 1994 to Feb 1998.	Patients with clinically progressive disease after chemotherapy were excluded.	No	None. CT was only performed after abnormal PET findings.	PENN-PET 240-H scanner (UGM, Philadelphia, PA). 6-8 mCi of FDG was administered intravenously, and scanning began 60-90 min later. Patients fasted for at least 6 hrs prior to scanning.	N/A	Positive predictive value of PET vs. CT (100% (6/60 vs. 42% (10/24)).
Buchmann et al. (2001)	Lymphoma	English Cancer	52 patients (27 HD, 25 NHL)	No	Regions of FDG uptake classified by site, intensity, size and shape. Any site exhibiting increased uptake was considered a suspected lymphoma.	Consecutive patients with a histologically confirmed diagnosis of untreated malignant HD.	Untreated diseases, with histologically proven diagnosis of HD or NHL, Oct 1996 to July 1998. Diabetics excluded.	PET scans interpreted by 2 experienced nuclear medicine physicians, CT scans by 2 independent radiologists, all in a blinded fashion.	Reference tests performed 4 weeks before or after PET and CT. Discrepancies between PET and CT verified by biopsy, MRI or clinical follow-up within the following 4 to 24 months.	Patients fasted for at least 12 hrs. Mean doses of 390 MBq of ^{18}F-FDG-PET and 20 mg of furosemide injected intravenously. Scanning began 60-90 min later.	25 additional lesions detected by PET. Nodal: 124 true positives identified by PET, 0 false positives, 1 false negative and 655 true negatives. 103 true positives by CT, 22 false negatives, 7 false positives and 648 true negatives. Extranodal: PET: 24 true positives, 349	PET: Nodal: 99.2% Extranodal: 100% Supradiaphragmatic: 99.1% Subdiaphragmatic: 100% CT: Nodal: 83.2% Extranodal: 80.8% Supradiaphragmatic: 80.3% Subdiaphragmatic: 91.2%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
											true negatives, 0 false negatives, and 3 false positives; CT: 20 true positives, 348 true negatives, 4 false positives, and 4 false negatives.	
Hueltenschmidt et al. (2001)	Lymphoma	English Cancer	81 patients	No	Any site exhibiting FDG uptake in the region of interest was considered representative of lymphoma manifestation.	81 patients with HD underwent 106 PET studies. 25 initial stagings, 63 evaluations of the response to therapy and 18 suspected recurrences.	Retrospective recruitment (Aug 1996 to April 2000).	Visual analysis of PET images by 3 experienced nuclear medicine physicians who had knowledge of the patients' clinical history.	Conventional imaging (mainly CT and sometimes MRI), biopsy and/or a very detailed clinical follow-up.	ECAT EXACT 47 scanner (Siemens/CTI, Knoxville, TN). Patients fasted for 12 hrs. Normal blood glucose levels confirmed in all patients prior to scanning. Mean FDG dose: 370 MBq.	63 PET studies for restaging in 51 patients. PET scans positive in 21/63 cases and negative in 42/63 cases.	Restaging group PET: 95 (95% CI: 89-100) Conventional imaging: 95 (95% CI: 89-100) Recurrence group: PET: 91 (95% CI:78-100) Conventional imaging: 91 (95% CI:78-100)
Jerusalem et al. (2000)	Lymphoma	English Haematologica	28 patients	No	PET images interpreted by a physician in the Division of Nuclear Medicine and reviewed by an investigator. Any region exhibiting higher-than-background uptake and/or excretion was considered positive for the	Consecutive patients with histologically confirmed NHL and who were scheduled for chemotherapy were included from May 1994 to March 1997.		Not mentioned.	None. Pre- and post-treatment evaluation.	Whole-body scan with a PENN PET 240-H camera 45-90 minutes after the intravenous injection of 200-300 MBq of ^{18}F-FDG. Patients fasted for at least 6 hrs prior to scanning.	5/28 patients with increased uptake. PET negative in 23/28 patients.	All 5 patients with and 7/21 without residual abnormal uptake relapsed or reprogressed.

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
					presence of tumor.							
Spaepen et al. (2001)	Lymphoma	English Jounral of Clinical Oncology	93 patients	No	Negative defined as no evidence of disease, positive as a site of uptake or any diffuse region of increased activity.	93 consecutive patients with histologically confirmed NHL. Retrospective analysis.	June 1995 to Sep 1993. Consecutive patients.	Clinical interpretation by 2 investigators blinded to the clinical data or CT findings.	Conventional diagnostic methods before and after therapy (CT, MRI and biopsy).	CTI/ Siemens ECAT 931 scanner. Patients fasted for at least 6 hrs, and blood glucose level measured prior to scanning. Dose of 370-555 MBq administered intravenously.	26 positive scans (persistent abnormal uptake) in 14/26 patients. Only PET detected persistent disease. 67 with negative scans (complete remission). Only 11 out of 63 relapsed.	
Tatsumi et al. (2001)	Lymphoma	English Journal of Nuclear Medicine	30 patients	No	Regions of FDG uptake classified according to site, intensity, size, shape and lateral asymmetry. Any site exhibiting higher-than-background FDG uptake and that was not located in a physiological region of uptake was considered positive for the presence of lymphoma.	Prospective recruitment.	Untreated or recurrent NHL confirmed by biopsy.	All the patients were randomized, and the results were read by 2 blinded nuclear medicine physicians.	CT scans obtained within the 2 weeks following FDG-PET.	Whole-body scan performed with Headtome V/SET 2400W camera. Fasting for at least 4 hrs. Scanning began 1 hr after the injection of 370 MBq of FDG. PET study with dual-head gamma camera (hybrid) equipped for coincidence emission performed on same day.	206 disease sites. Hybrid and dedicated scanners detected 159 sites and 179 sites, respectively. CT and ^{67}Ga: 164.	Hybrid PET: 77.2% PET: 86.9% CT and ^{67}Ga: 79.6%.

A8.6 BREAST CANCER

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Cook and Fogelman (1999)	Breast – skeletal metastases	English Seminars in Nuclear Medicine	< 10	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Crippa et al. (1997)	Breast cancer metastases	English Tumori	66 patients who underwent axillary node dissection and 16 who did not.	No	Increased uptake was considered abnormal and interpreted as pathologic.	Not stated.	Not stated.	Not mentioned.	PET results were compared with the pathology findings at surgery.	PET studies performed 1-7 days prior to surgery using a GE 4096 WB Plus scanner. Scanning began 45-60 min after injection of FDG.	31 with axillary metastases, 52 without axillary metastases.	PET in the detection of axillary metastases: 84% Palpable nodes vs. non-palpable nodes: 92% (11/12) vs 79% (15/19)
Cowen (1998)	Breast cancer metastases	French Cancer/Radiotherapie	908 patients who received surgery and radiotherapy but no chemotherapy.	No	No	Patients were divided into two groups, based on the tumor resection margins.	Patients selected retrospectively, 1980 to 1995.	N/A	Pathology.	N/A	N/A	N/A
Noh et al. (1999)	Breast cancer	English Eur J Surg	8 patients with breast implants (of 59 who underwent PET) (6 patients had paraffin implants, the other 2 silicone implants).	No	Standardized uptake value (SUV). Relative uptake values expressed as a percentage of the baseline PET scan.	All examined at a local hospital and sent to Seoul National University Hospital	Patients who underwent PET from June 1995 to Nov 1997.	PET images were assessed and documented before the surgical and histopathology results were available.	Physical exam, mammography and tumor histology.	ECAT EXACT 37 scanner. 370 MBq of FDG was injected intravenously in each patient 60 min prior to scanning.	N/A	N/A
Crippa et al. (1998)	Breast cancer	English Journal of Nuclear Medicine	68 females patients (age: 29 to 84).	No	Images were considered positive in the presence of increased localized FDG uptake in relation to the surrounding tissue. Semiqua	Consecutive patients scheduled for surgery and axillary lymph node dissection.	All consecutive patients included.	PET interpretations blinded to the histopathology findings at surgery.	Pathology reports were the basis for the final classification of the nodules.	400 MBq of FDG was injected into a vein contralateral to the tumor side, patients fasted for at least 5 hrs and all had normal glucose levels.	27 with axillary metastases, 45 without axillary metastases. With N_0: 10 Without N_0: 26 With N_{1a}: 8 Without N_{1a}: 13 With N_{1b-2}: 9 Without N_{1b-2}: 6	PET in detecting axillary metastases: 85% Clinical axillary stage of the N_0 patients: 70% N_{1a} patients: 85.5% N_{1b-2} patients: 100%

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivit
					ntitative analysis of FDG uptake was performed by generating parametric images of standardized uptake values (SUVs) in which the concentration of radioactivity was divided by the ratio of total administered activity to body weight.					PET performed 1-7 days prior to surgery with GE4096 WB Plus scanner.		
Raylman et al. (2000)	Breast cancer	English Med. Phys.	No subjects (simulated breast tissue).	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

A8.7 PROSTATE CANCER

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Seltzer. et al. (1999)	Prostate cancer	English Journal of Urology	45 patients with an elevated PSA were studied following prostatectomy, radiation therapy or cryosurgery.	No	Visual analysis. PET and monoclonal antibody scan were interpreted, on different days, by consensus of 2 nuclear medicine physicians, who were therefore not blinded to one another but who were	Aug 1996 to Jan 1998	Patients with an elevated PSA.	CT readings were blinded to the results of PET and monoclonal antibody scan. PET and monoclonal antibody scan were blinded to CT but not totally to each other.	CT. Interpreted by genitourinary radiologist.	Patients fasted prior to scanning. 12-15 mCi of FDG given to image glucose metabolism. A Siemens HR 961 or 962 scanner was used.	N/A	Data not given.

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
					blinded to the CT findings.							

A8.8 MISCELLANEOUS USES (NOT EXAMINED IN THIS REPORT)

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Lips et al. (2000)	Thyroid cancer metastases	English Netherlands Journal of Medicine	Case reports of 4 patients.	No	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Barkheet et al. (1999)	Benign esophageal disease	English Clinical Nuclear Medicine	Case reports of 3 patients.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Flamen et al. (2000)	Esophageal carcinoma	English Journal of Clinical Oncology	74 patients with esophageal or gastroesophageal carcinoma.	No	Blinded visual analysis of the transaxial, coronal and sagittal planes. High-resolution display monitor.	All referred for evaluation of the operability of an esophageal tumor.	Exclusion criteria: previous treatment for esophageal cancer, diabetes, pulmonary inflammatory disease or inoperability for medical reasons.	Yes	All patients had an ultrasound of the neck, a barium x-ray of the esophagus, a bronchoscopy, a spiral CT scan of the chest and abdomen and transesophageal endoscopic ultrasound (EUS).	CTI/Siemens 931/08/12 scanner. Image transmission before the injection of 6.5 MBq/kg of FDG; max. of 555 MBq. Scanning began 60 min after injection. 5 bed positions.	With disease: 34 patients, stage IV disease. Without disease: 40 patients	Detection of stage I disease in 74 patient PET: 74% Ultrasoun 41% CT: 42% CT + ultrasound: 47 All compared to th diagnostic standard: histology lymph nodes wit malignant tumors PET: 39% Ultrasoun 63% CT: 22% CT + ultrasound: 54
Meltzer et al. (2000)	Esophageal cancer	English Clinical Nuclear Medicine	47 patients referred for initial staging of esophageal cancer prior to minimally invasive	No	Visual analysis by 2 nuclear medicine specialists. Divergent evaluations.	New diagnosis of esophageal cancer, University of Pittsburgh.	Patients evaluated between July 1995 and March 1998. 67 eligible, 10 excluded because of ad-	Yes. 20 PET studies in other patients with nonesophageal thoracic cancer selected	CT data evaluated by experienced radiologists blinded to all the clinical data, except the diagnosis	Patients fasted for at least 4 hrs. Injection of 7 mCi of FDG. Scanning began 45-60 min later. ECAT	Primary tumor. With: 47 Without: 20 Nodal staging: With: +: 35 -: 36 Without:	PET findings: Primary tumor + equivocal findings: 87% - equivoca findings: 79% Nodal staging

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
			surgical staging.				vanced disease, and 10 other excluded for technical reasons.	for inclusion in the analysis of the PET findings. Reading blinded to clinical data.	of esophageal cancer.	ART scanner.	+: 12 -: 11 Distant metastases: With: 10 Without: 36	+ equivocal findings: 43% - equivoca findings: 39% Distant metastases + equivocal findings: 70% - equivoca findings: 30%
Choi et al. (2000)	Esophagus (squamous cell carcinoma)	English Journal of Nuclear Medicine	48 patients with a diagnosis of histologically proven primary esophageal carcinoma (45 men and 3 women).	No	Visual analysis.	All consecutive patients eligible.	61 consecutive patients with a diagnosis of histologically proven primary esophageal carcinoma (Feb 1997 to Dec 1998). 13 patients excluded because they did not undergo an esophagectomy.	Yes. The PET findings were interpreted, by consensus, by 2 nuclear medicine physician blinded to the CT, endoscopic ultrasound and histology results.	CT (HiSpeed Advantage scanner). Images interpreted before surgery by a radiologist blinded to the PET, endoscopic ultrasound (EUS) and histology results. EUS performed in all but 3 of the patients (could not tolerate the procedure) and interpreted by a gastroenterologist blinded to the PET, CT and histology results. EUS incomplete in 12/45 patients.	Advance PET scanner (GE Medical Systems). Scanning began 45 min after the injection of 370 MBq of FDG. Images reconstructed without attenuation correction.	100 lymph node groups with metastases. 282 groups negative. Region (+) chest: 62 abdomen: 30 neck: 8 Region (-) chest: 181 abdomen: 85 neck: 16	PET: 57% (for determining if there is metastasis to individual lymph node groups) CT: 18% Difference between PET and CT: $p<0.001$ Anatomic: region of metastases (PET): Thoracic lymph nod groups: 66.1% Abdomina lymph nod groups: 46.7% Cervical lymph nod groups: 37.5%
Stumpe et al. (2000)	Soft tissue and bone infections	English Eur J Nucl Med	39 patients with suspected infections	No	Visual analysis by 2 blinded nuclear	Yes	Patients referred for evaluation of	36 patients had CT or MRI within 3	No	GE Advance PET scanner. Patients	With disease: 24 in soft tissues. 16 in	Patients with soft tissue disease: 96% Bone in-

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
			(cause of infection: patients were either not taking their antibiotics or not responding to therapy).		medicine physicians.		suspected infection.	days after PET, or comparison made with histology findings.		fasted for at least 4 hrs and received an intravenous injection of 300-400 MBq of FDG that had been produced in-house 30-40 min earlier using a 17.8-MeV cyclotron.	bone. 40 pooled with disease. Without disease: 3 in soft tissues. 9 in bone. 12 pooled without disease	fections: 100% Pooled: 9
Schulte et al. (2000)	Skeletal tumors	English Journal of Nuclear Medicine	202 patients with primary bone tumors.	No	Qualitative and semi-quantitative analysis of the areas of elevated FDG uptake. T/Bs (tumor-to-background ratios) obtained by 2 physicians blinded to each other and to the clinical data and averaged for statistical analysis.	Ongoing prospective study that began in 1993.	Patients with radiographic evidence of an active benign lesion, aggressive benign lesion or malignant primary bone neoplasm.	Blinded to clinical data.	Incisional, excisional or needle biopsy performed within 8 days after PET.	ECAT 931-08-12 scanner (Siemens /CTI). Patients fasted for at least 8 hrs, and blood glucose measured and recorded before injection of FDG. Dose depended on body mass: 120-300 MBq.	With malignant disease: 115 With benign disease: 87	PET: 93% (Using a T/B cut-of level of 3.0).
Barkheet et al. (1998)	Tuberculosis	English Clinical Nuclear Medicine	Case reports of two patients.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Barkheet et al. (2000)	Breast infection and inflammation	English Clinical Nuclear Medicine	Case reports of two patients.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

Table 32: Selection of studies on PET (neurology)

A8.9 ALZHEIMER'S DISEASE

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Reiman et al. (2001)	Alzheimer's disease	English Proc Natl Acad Sci USA	4 heterozygotes and 4 noncarrier controls matched for sex, age and education. 2 years later, 10 heterozygotes and 15 noncarrier controls.	No	N/A	Volunteers recruited by newspaper advertisements. Had a family history of Alzheimer's disease with at least one 1st-degree relative affected.	N/A	N/A	N/A	ECAT 951/31 scanner. Intravenous injection of 10 mCi of 18-FDG.	N/A	N/A
Kawano et al. (2001)	Alzheimer's disease	English Dementia and Geriatric Cognitive Disorders	26 patients with slowly progressing memory problems.	No	PET used to measure the regional cerebral metabolic rate of glucose (rCMRglc).	Probability or possibility of Alzheimer's disease. Patients admitted to hospital for approx. one week.	N/A	N/A	N/A	N/A	N/A	N/A

A8.10 REFRACTORY EPILEPSY

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Dupont et al. (2000)	Epilepsy	English Arch Neurol	30 patients	No	Calculation of the asymmetry index.	30 consecutive patients with temporal lobe epilepsy who had undergone surgery and who had different postoperative health outcomes.		Not mentioned.	None: surgery	ECAT 953/31B scanner (CTI/ Siemens). 31 transversal sections of the brain 30 min after the intravenous injection of FDG at a mean dose of 29.6 x 10[illegible].	2 years after surgery: 14 seizure-free, 10 mostly improved and 6 with persistent seizures.	

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Muzik et al. (2000)	Epilepsy	English Neurology	10 patients	No	Semiautomated software for defining abnormal supratentorial cortical areas in PET images.	Mostly pediatric patients with refractory extratemporal epilepsy.	Not stated.	Not mentioned.	FMZ-PET, intracranial EEG.	Patients fasted for 4 hrs before the scanning PET performed during the interictal state. CTI/Siemens ECAT/HR scanner. Scanning began 30 min after the injection of FDG (0.143 mCi/kg).	Data not given.	Detection of epileptogenic foci: FMZ at 10% threshold: 81 ± 9% 12% threshold 57 ± 10% 15% threshold 37 ± 12%. FDG at 10% threshold 53 ± 13% (p=0.06) 12% threshold: 32 ± 12% (p=0.03) 15% threshold: 16% ± 6% (p=0.08). Detection of cortical areas of seizure spread 10% threshold FMZ: 31 ± 9%; FDG: 34 ± 9% (p=0.51) 15% threshold FMZ: 19 ± 8%, FDG 10 ± 6% (p=0.28) Regions o interictal spiking 10% threshold 80 ± 7% f FMZ, 57 ± 13% for FDG (p=0.15)
Tatlidil et al. (2000)	Epilepsy	English Acta neurol. Belg.	35 patients, 100 controls (75 ^{15}O-water, 25 FDG).	No	Mean index of metabolic symmetry calculated. Abnormal PET findings divided into 3 groups: mild, moderate	35 patients who had had an anterior temporal lobectomy for complex partial seizures.	Referred by 3 centres.	Not mentioned.	MRI, electroencephalographic video monitoring with recording of seizures, and neurological examina-	GE/Scanditronix scanner. Bolus of 2,405-2,960 MBq of ^{15}O-water administered for each recording after blood	Histopathologic abnormalities observed in 30 patients. 15 patients had hippocampal sclerosis. After a temporal lobec-	PET of blood flow 80% Patients with normal MRI: FDG-PET 78% PET of blood flow 64% Visual analysis of

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
					and severe.				tion.	flow imaging. 204 MBq of FDG injected.	tomy, 20 patients were seizure-free, 13 showed significant improvement and 2 did not show significant improvement.	MRI: 60% (detection of lesions)
Ryvlin et al. (1998)	Epilepsy	English Brain	100 patients and 12 controls.	No	Qualitative analysis reviewed by 2 independent PET experts.	100 consecutive patients with refractory epilepsy	Prospective inclusion of 100 consecutive patients referred to the centre for medically refractory partial epilepsy.	Yes. PET interpretations blinded to the other data.	MRI, FMZ-PET, video ECG monitoring.	FMZ- and FDG-PET performed on the same day in 90 patients with a time-of-flight device (TTV03, LETI, CENG). FDG-PET performed 90 min after the last injection of FMZ. Methods described elsewhere.	Temporal lobe epilepsy (n=52): Nonlateral mesiotemporal sclerosis MRI (n=30) Detection by MRI 30/30 FDG-PET 29/30 FMZ-PET 30/30	FMZ-PET 73% MRI: 66%
Hwang et al. (2001)	Epilepsy	English AJNR Am J Neurol	117 patients (103 underwent PET, 93 interictal SPECT and 91 ictal SPECT.	No	Visual and qualitative interpretation.	Consecutive patients who underwent surgery for intractable neocortical epilepsy.	Review of 358 medical records, including those of 117 patients with neocortical epilepsy.	Blinded reinterpretation.	SPECT, MRI, pathology.	ECAT EXACT scanner. Scanning performed 60 min after the injection of 370 MBq of 18-FDG during the interictal period.	117 patients in all (pathologic diagnosis: 50 temporal, 33 frontal, 15 occipital, 13 parietal, 2 hemispheric, 4 multifocal); 77 neuronal migration disorder (pathologic diagnosis: 28 temporal, 25 frontal, 10 occipital,	Overall rat of correct localizatio of epilepto genic foci: MRI: 59.8% PET: 77.7% Ictal SPECT: 70.3% For patient with an adequate postoperative follow up: MRI: 65.5% PET: 77.2% Ictal SPECT: 73.8% Rate of co

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
											10 parietal, 2 hemispheric, 2 multifocal), 15 tumors (pathologic diagnosis: 13 temporal, 1 occipital, 1 multifocal) and 25 others (9 temporal, 8 frontal, 4 occipital, 3 parietal, 1 multifocal).	rect localization of temporal neocortica epilepsy: MRI: 64.0%, PET: 86.7% Ictal SPECT: 0.6%) Extratemporal: MRI: 56.7%, PET: 70.7% Ictal SPECT 63.6%

A8.11 BRAIN TUMORS (MAINLY GLIOMA)

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
Bader et al. (1999)	Suspected recurrences of glioma	English Eur J Nucl Med	30 patients who were part of a larger group of patients referred consecutively because of suspected recurrence or for grading after initial treatment.	No	Visual analysis in axial, coronal and sagittal planes with a reversed gray scale and a quantitative analysis of the PET results selected for analysis of the regions of interest, based on a standardized gray scale.	Patients with suspected recurrence and scheduled for further treatment. Initial treatment ended at least 6 months before the PET study.	9 patients with an initial diagnosis of grade II astrocytoma, 10 with grade IV glioma, 3 with grade II oligoastrocytoma, 6 with grade II oligodendroglioma and 2 with grade III oligodendroglioma.	2 independent observers blinded to the clinical and histopathology data, classified the PET and SPECT images as positive or negative.	SPECT, stereotactic biopsy.	ECAT ART camera (Siemens/CTI, USA). 12-hour overnight fast. Admin. of 200 MBq of FDG. Transaxial images reconstructed with filtered back-projection and corrected for attenuation (see ref. for details).	29 recurrences and 1 nontumor lesion (postoperative scar).	SPECT 100% for grade IV, 86% for grade III, 75% for grade II. PET 100% for grade IV, 71% for grade III, 50% for grade II.

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
DeWitte et al. (2001)	High-grade astrocytoma	English J Neurooncol	91 patients (30 with grade III multiform glioblastomas, 61 with grade IV glioblastomas).	No	Qualitative analysis using the following grading scale: 1, uptake lower than in the contralateral white matter; 2, uptake intermediate between the contralateral white matter and cortex; and 3, uptake greater than or equal to that in the contralateral cortex.	Patients with high-grade glioma proven histologically for prognosis.	91 patients studied, but analysis concerned only 26 patients because of deaths (n=50) or follow-up not done (n=15).	2 independent observers interpreted the PET scans visually.	None	Siemens/CTI 933/08-12 scanner with 6.75-mm sections. Attenuation correction. IV injection of 260 MBq of FDG, with scanning beginning 40 min later.	8 patients: grade I 42 patients: grade II 41 patients: grade III	No data given
Derlon et al. (2000)	Oligodendrogliomas	English Eur J Nucl Med	47 patients with histologically confirmed oligodendrogliomas (27 low-grade; 20 high-grade).	No	Histology slices reviewed by the same pathologist: regions of interest, visual analysis. Mean tumor/healthy tissue ratio for ^{11}C-MET and FDG; min. and max. ratio for each slice; standard deviation for the ratio values and the total volume	Not given.			CT, MRI and ^{11}C-MET PET.	LETI TTV03 scanner with high transaxial resolution, 7 planes, attenuation correction based on transmission with ^{68}Ge. After June 1996: ECAT HR+ scanner (Siemens/CTI).		No data given.

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
					of the integrated regions of interest for the different slices.							
Eary et al. (1999)	Malignant brain tumors	English Cancer Res	13 patients	No	Patients underwent closely spaced ^{18}F-FDG/^{11}C-dThd + MRI. Image results compared by standardized visual analysis. Grading by 2 experienced observers. Qualitative analysis. 0 = uptake less than or equal to that of normal tissues 1 = minimally abnormal uptake 2 = uptake definitely abnormal Comparison of results: dThd vs. FDG dThd vs. IRM FDG vs. MRI	Primary or recurrent brain tumors. Patients referred for PET scanning by the University of Washington Medical Centre.		Not mentioned	2-[C-11]thymidine (dThd), PET, MRI.	Imaging by ^{11}C-dThd followed by ^{18}F-FDG PET. Blood sample. 10 to 20 mCi 2-[C-11]dThd injected IV for 60 seconds with Harvard infusion pump. GE-Advance scanner. Image reconstruction by 3-D reprojection algorithms. With transversal and axial filters (more details in article). Imaging by FDG-PET after ^{11}C. 10 mCi of FDG administered IV with Harvard pump for 2 min. Blood sample (glucose).	4: multiform glioblastoma 7: anaplastic astrocytoma 1: peripheral neuroectodermal tumor 1: cystic adenoid carcinoma	No data given.
Nuutinen	Astrocyto	English	14 pa-	No	Stan-	Newly		Yes.	MRI/CT	425 MBq	Data not	Data not

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
et al. (2000)	mas	Int J Radiat Oncol Biol Phys	tients: 13 with low-grade astrocytomas, 1 with multiform glioblastoma.		dardized uptake value and tumor/contralateral brain SUV ratios. Visual and quantitative analyses. All images showing areas of increased MET uptake in the tumor region were considered positive on visual analysis.	diagnosed or recurrent low-grade tumors.		Blinded reading by 2 oncologists/radiologists guided by the MRI results or with knowledge of the MRI + CT results as well as the clinical data on the patients.		of ^{11}C-methionine. Patients fasted for 5 hrs. ECAT 931/08 scanner (Siemens/CTI). 15 6.7-mm slices. Images reconstructed according to MRI. Attenuation correction with ^{68}Ge. Scanning began 20 min after injection.	given.	given.
Sato et al. (1999)	Ghomas	English Abstract Neuroxsurg Rev	13 patients							^{11}C-methionine PET.		
Stokkel et al. (1999)	Recurrent brain tumor	English Abstract Nucl Med	16 patients		Quantitative analysis with thallium index and	Suspected recurrent brain tumor.			SPECT	SPECT et PET performed on the same day. Coinci-	12 with recurrence.	SPECT: 92% PET: 62% (p= 0.023)

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
		Commun			FDG index. Also, visual assessment.					dence detection camera.		
Thompson et al. (1999)	Recurrent tumors	English Abstract Stereotact Funct Neurosurg	15 patients								14 with disease, 1 without	PET: 43%
Roelcke et al. (1999)	Low-grade astrocytomas	English J Neurol Neurosurg Psychiatry	30 patients		Visual analysis of the regions of interest/quantitative analysis of radioactivity concentration ratios in tumors (T) over contralateral brain (C) (T/C).		Patients who did or did not receive radiation therapy subsequent to first tumor resection.	Not mentioned	FDG compared with MET.	CTI scanner (933/04-16) MET: 35 min after injection. FDG: 48 min after injection. The two tests were performed 3 to 4 hrs apart.		In patients who had received radiation therapy (n=13): MET T/C: 1.31 (0.42 FDG T/C: 0.90 (0.16 In patients who did n receive radiation therapy (n 17): MET T/C: 1.33 (0.40 FDG T/C: 0.82 (0.10 Malignant progressio (yes, n=7) MET 1.70 (0.64);

Study	Site	Language and source	Size of patient sample	Duplicate study?	Type of PET analysis	Inclusion criteria	Inclusion	Blinded reading?	Reference test	PET methods	Patients with/without disease	Sensitivity
												FDG 0.98 (0.23) (no; n=13) MET 1.21 (0.21); FDG 0.82 (0.08)

A8.12 MYOCARDIAL VIABILITY

Table 33: Selection of studies using a clinical criterion as an assessment criterion and studies on changes in management due to PET scan results (cardiology)

Study	Methodological quality (grade)	Number of patients Age Mean duration of follow-up	LVEF	Assessment criterion	Groups	Results
Eitzman et al., 1992 Retrospective	C	82 59 ± 10 years 12 months	34 ± 13%	Composite (deaths, cardiac arrests, MIs, late revascularization)	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization) and PET results.	Significantly more deaths in the group with viabl treated medically.
Yoshida et al., 1993 Retrospective	C	35 54 years 3 years	43.6%	Death	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization) and PET results.	No significant difference in mortality between th Mortality lower in the patients with viable myoc
Tamaki et al., 1993 Retrospective	C	84 58 ± 9 years 23 ± 12.7 mos	50 ± 12% (group without events) 42 ± 14% (group with events)	Composite (deaths, MIs, angina, late revascularization).	Comparison of medically treated patients with and without viability.	FDG uptake is a predictor of events.
Lee et al., 1994 Retrospective	C	129 62 ± 11 years 17 ± 9 months	38 ± 16%	Composite (CV events + deaths).	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization) and PET results.	The patients with viable tissue who were treated ischemic events (48%) than the patients with vial revascularized (8%, $p<0.001$). Cox analysis: Viability and no revascularization only age and EF, not viability, are predictors of d
Di Carli et al., 1994 Retrospective	C	93 65 ± 10 years 13.6 months	28 ± 6%	Mortality	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization) and PET results.	The patients with viable myocardium who under higher 1-year survival rate than those treated mec
Di Carli et al., 1995 Prospective	C	36 66 ± 8 years 25 ± 14 mos	28 ± 6%	Improvement in heart failure symptoms.	All the patients were revascularized.	There was greater functional improvement in the cardium as detected by PET.
Haas et al., 1997 Retrospective	B	69 PET group: 60 ± 10 years Non-PET group: 63 ± 9 years 12 months	≤ 0.35%	Survival at 12 months after revascularization.	Comparison of patient outcomes with respect to performing or not performing PET. 35 PET patients 34 non-PET patients	12-month survival rate: 97% with PET vs. 79% v In-hospital mortality: PET, 0; other group, 11.4%
Beanlands et al., 1997	B	80	81 pts < 50% 41 < 30%	Change in management.		Change in management strategy in 57% of the ca the LVEF was < 30%.
Vom Dahl et al., 1997 Prospective	B	161 57 ± 9 years 29 ± 6 months	45 ± 12%	Composite + changes in symptoms.	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization) and PET results.	Among the patients who were revascularized, on on PET had a significant decrease in the number Improvement in symptoms in the patients with vi vascularized in relation to those who were treate
Pagano et al., 1998	C	35	23.6%	Change in	All the patients were	Correlation between the number of viable segme

Retrospective		45 to 72 years 6 months		LVEF, exercise capacity, and quality of life.	revascularized.	LVEF. No correlation with exercise capacity or c
Di Carli et al., 1998 Retrospective	C	93 69 years Median follow-up of 4 years	Median: 25%	Survival at 4 years.	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization) and PET results.	In patients with viability on PET: 4-year survival rate with medical treatment: 30%
Schelbert et al., 1998 Retrospective	C	112 evaluated for cardiac transplantation	≤ 35%	Survival at 5 years.	Comparison of patient outcomes with respect to treatment (medical treatment, revascularization, transplantation) and PET results.	5-year survival rate: 80% in the group with viable myocardium that w 71.4% in the group without viable myocardium t 42% in the group without viable myocardium tha
Landoni C et al., 1999 Retrospective	C	241 (153 evaluated by PET)	29.8 ± 6.7%	Survival at 30 days.	Comparison of outcomes in the revascularized patients with respect to PET scan results.	30-day mortality rate: 0.9% in the PET group. 19.8% in the group that was not assessed by PET Only predictor of perioperative outcome: presenc tion fraction.
Marwick et al., 1999 Prospective	B	63 66 ± 9% 17 months	28 ± 7%	Survival, functional capacity, quality of life.	All the patients were revascularized.	Myocardial viability is a predictor of the improve of quality of life.
Siebelink et al., 2001 Prospective	A	103 28 ± 1 months		Cardiovascular event-free survival.	Comparison of the groups managed in light of the of PET results vs. SPECT results.	No difference between the two groups.

Table 34: Selection of studies of the use of PET, using an intermediate criterion as an assessment criterion (cardiology: functional reversibility of segmental wall motion)

Study	Patients (n)	LVEF	Sensitivity (%)	Specificity (%)	PPV (%)
Tillisch et al., 1986	17	32 ± 14%	95	80	85
Tamaki et al., 1989	22	NR	78	78	78
Tamaki et al., 1991	11	NR	100	37	80
Carrel et al., 1992	23	34 ± 14%	94	50	84
Lucignani et al., 1992	14	38 ± 5%	93	86	95
Gropler et al., 1992	16	NR	79	83	79
Manwick et a., 1992	16	NR	71	76	68
Vanoverschelde et al., 1993	12	55 ± 7%	100	-	100
Gropler et al., 1993	34	NR	83	50	52
Maes et al., 1994	20	48 ± 9%	82	67	75
Knuuti et al., 1994	48	53 ± 11%	85	84	70
Vom Dahl et al., 1994	37	34 ± 10%	66	77	53
Grandin et al., 1995	25	49 ± 11%	88	50	79
Tamaki et al., 1995	43	41	88	82	76
Gerber et al., 1996	39	33 ± 10%	75	67	
Bax et al., 1996	17	36 ± 11%	PET: 89 Thallium-201: 93 Echo stress 85	PET: 77 Thallium-201: 43 Echo stress: 63	PET:62 Thallium-201: 40 Echo stress: 49
Vom Dahl et al., 1996	52	47 ± 10%	95	73	68
Baer et al., 1996	42	40 ± 13%	PET: 96 Echo stress: 92	PET: 69 Echo stress: 88	PET: 72
Maes et al., 1997	30	46.5%	-	-	PET: 91 MIBI SPECT: 82
Wolpers et al., 1997	30	42 ± 11%	-	-	78
Pagano et al., 1998	30	25 ± 7%	PET: 99 Echo stress: 61	PET: 33 Echo stress: 63	PET: 66 Echo stress: 68
Fath-Ordoubadi et al., 1998	47	≤ 30%			63 to 81, depending o the FDG uptake cut-o level.
Zhang et al., 1999	60	44 ± 15%	76	86	88
Rossetti et al., 1999	17	52.5 ± 7%	PET 87	PET 26.3	PET: 45,7 MIBI SPECT: 46.5 THALLIUM SPECT: 47.4

Study	Patients (n)	LVEF	Sensitivity (%)	Specificity (%)	PPV (%)
Kitsiou et al., 1999	26	31 ± 8%			65 to 76, depending o the FDG uptake cut-o level.
Pasquet et al., 2000	66 Global LV function	28 ± 5%	PET: 56 Echo stress: 94	PET 64 Echo stress: 59	
Wiggers et al., 2000	46	35 ± 7%	PET: 81 Echo stress: 51%	PET: 56 Echo stress: 98	
McFalls et al., 2000	20 Global LV function	≤ 27%			67

Appendix 9

Methodological Quality of Studies

APPENDIX 9: METHODOLOGICAL QUALITY OF STUDIES

Table 35: Methodological Quality of Studies – Lung Cancer

STUDY	STUDY FEATURES	COMMENTS
Erasmus et al., 2000	- Small sample (25 cases: 18 men; age: 37 to 86). - Retrospective design (unit of analysis: the patient). - All eligible patients included in analysis. - Diagnosis defined by appropriate reference standard. PET procedure adequately described; no mention of blinded reading. - PET not compared with conventional imaging.	**Grade C** - Small sample, no mention of blinded reading. - No comparison of sensitivity and specificity rates with those of conventional imaging methods. - Retrospective design.
Gupta et al., 2000	- Large sample (118 cases: 73 men; age: 35 to 84 years). - Consecutive cases (unit of analysis: the nodal station). - All eligible patients included in the study, but only 54 cases included in the analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; blinded reading of images. - PET compared with CT.	**Grade B** - Certain cases excluded from the analysis (only 54 of the 118 cases were included). - Resection based on staging by PET + CT.
Vanuytsel et al., 2000	- Large sample (105 cases; sex and age distribution not given). - Retrospective design (unit of analysis: the nodal station). - All eligible patients included. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT and PET + CT.	**Grade B** - Overlapping of cases with those from two previously published studies.
Dewan et al., 1997	- Adequate sample (52 cases; age > 30 years; sex distribution not given). - Retrospective design with consecutive cases (unit of analysis: the nodal station). - All eligible cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET not compared with conventional imaging.	**Grade C** - Referred cases from the same institutions as the cases in a previous study by Dewan et al. (1995). - No comparison between PET and conventional imaging. - Retrospective design.
Marom et al., 1999	- Large sample (100 cas: 58 men; age: 25 to 83). - Prospective design; consecutive cases (unit of analysis: the patient). - 39 of the 139 the initial consecutive patients excluded from the study, but the 100 remaining cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT.	**Grade A**

STUDY	STUDY FEATURES	COMMENTS
Patz et al., 1995	- Adequate sample (42 cases: 26 men; age: 25 to 85). - Prospective design (unit of analysis: the nodal station). - Not all the eligible patients were included in the study, but all who were included in the study were also included in the analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT.	**Grade B** - Adequate sample, but small. - Not all the eligible patients were included in the study.
Vansteenkiste *et al.*, 1998	- Adequate sample (68 cases; age: 40 to 83; sex distribution not given). - Prospective design (unit of analysis: the nodal station). - Not all the eligible patients were included in the study, but all who were included in the study were also included in the analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - Comparison between PET + CT and CT alone.	**Grade B** - Not all eligible patients were included in the study. - Comparison between CT and PET + CT but not with PET alone. - Overlapping of cases in this study with those in 1997 study by the same authors.
Vansteenkiste et al., 1997	- Adequate sample (50 cases: age: 40 to 83 sex distribution not given). - Prospective design (unit of analysis: the patient). - Not all the eligible patients were included in the study. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT alone and with PET + CT.	**Grade B** - Not all eligible patients were included in the study. - Overlapping of cases with those in a subsequent study by the same authors (1998).
Pieterman et al., 2000	- Large sample (102 cases: 88 men; age: 25 to 77). - Prospective design, consecutive cases (unit of analysis: the patient). - All eligible cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT alone and with PET + CT.	**Grade: A**
Roberts et al., 2000	- Large sample (100 cases; age and sex distribution not given). - Retrospective design (unit of analysis: the patient). - All eligible cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; no mention of blinded reading. - PET not compared with conventional imaging.	**Grade C:** - Retrospective design. - No mention of blinded reading. - PET not compared with conventional imaging. - The cases were patients referred to the study – possibility of selection bias.

STUDY	STUDY FEATURES	COMMENTS
Hara et al., 2000	- Small sample (29 cases: 19 men; age: 40 to 83). - Retrospective design (unit of analysis: the nodal station). - All eligible cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - FDG-PET compared with CT and C-choline PET.	**Grade C** - Small sample. - Retrospective design.
Weber et al., 1999	- Small sample (27 cases: 26 men; mean age: 62 ± 9). - Retrospective design (unit of analysis: the patient). - All eligible cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT and coincidence imaging (coincidence gamma camera).	**Grade C** - Small sample. - Cases with disease only. - Retrospective design.
Berlangieri et al., 1999	- Adequate sample (50 cases: 37 men; age: 41 to 78). - Consecutive cases (unit of analysis: the nodal station). - All eligible cases included in the study and analysis. - Diagnosis defined by appropriate reference standard. - PET procedure adequately described; images evaluated independently. - PET compared with CT.	**Grade B** - Size of patient sample.
Saunders et al., 1999	- Large sample (97 cases: 64 men; age: 36 to 77). - Consecutive cases (unit of analysis: the nodal station). - Diagnosis defined by appropriate reference standard. - All eligible cases included in the study, but only 84 were included in the analysis. - PET procedure adequately described; images evaluated independently. - PET compared with CT.	**Grade B** - Not all the cases were included in the analysis. - Cases referred to the study (possibility of selection bias).
Magnani et al., 1999	- Small sample (28 cases: 26 men; age: 50 to 75). - Retrospective design (unit of analysis: the patient). - Diagnosis defined by appropriate reference standard. - All eligible cases included in the study and analysis. - PET procedure adequately described; images evaluated independently. - PET compared with CT alone and with PET + CT.	**Grade C** - Small sample. - Retrospective design.

Table 36: Methodological Quality of Studies – Colorectal Cancer

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Valk et al., 1999	Cancer colorectal	English Arch Surg	Include	Inclusion/exclusion criteria clearly stated. PET and CT images read at the same time by 1 or 2 investigators with access to the clinical data. Ambiguous.	A
Imdahl et al., 2000	Metastases from colorectal cancer	English Langenbeck's Arch Surg	Include	Inclusion/exclusion criteria not clearly stated (consecutive patients?). Circular reference standard.	C
Zhuang et al., 2000	Hepatic metastases from colorectal cancer	English Nucl Med Comm	Include	Direct comparison: PET/surgical pathology/clinical follow-up – blinded reading of results???? Performed within 8 weeks of conventional imaging. 80 consecutive patients (retrospective).	B
Staib et al., 2000	Recurrent colorectal cancer	English Am J Surg	Include	Prospective recruitment. Inclusion/exclusion criteria clearly stated. PET scans evaluated independently, with readers blinded to results of conventional imaging but with knowledge of diagnosis and indication. Reference standard somewhat circular.	B
Willkomm et al., 2000	Recurrent colorectal cancer	English J Nucl Med	Include	Blinded reading of scans with conventional imaging. Recurrent disease detected in only 9 patients (small sample). Prospective recruitment.	C

Table 37: Methodological Quality of Studies - Melanoma

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Paquet et al., 2000	Metastatic melanoma	English	Include	Small sample (24 patients).	D

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
		Dermatology		Comparison between PET and conventional imaging. Blinded reading? No mention. Inclusion/exclusion criteria not clearly stated. PET not compared with conventional imaging.	
Eigtved et al., 2000	Metastatic melanoma	English Eur J Nucl Med	Include	Consecutive patients. PET scans visually interpreted. PET compared with conventional imaging and clinical examination.	C
Acland et al., 2000	Metastatic melanoma	English J Am Acad Dermatol	Include	PET compared with histology. Patients referred for PET for various reasons. Patients identified retrospectively in a PET database. PET not compared with conventional imaging.	C
Krug et al., 2000	Metastatic melanoma	English Acta Radiologica	Include	Consecutive patients studied retrospectively. No sensitivity/specificity data.	C
Wagner et al., 1999	Melanoma	English J Clin Oncol	Include	Prospective study. Methodology adequately described. Inclusion/exclusion criteria not clearly stated. PET scans interpreted in a blinded fashion by a single investigator. 74 patients.	A
Jadvar et al., 2000	Melanoma	English Clin Nucl Med	Include	Retrospective chart review. Small sample (38 patients). Reading done by a single observer who was aware of the clinical changes and previous radiographic results. No sensitivity/specificity data.	D
Dietlein et al., 1999	Melanoma	English Nucl Med Comm	Include	68 patients (small number in the analysis). No protocol for time or extent of the examination.	D

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
				PET scans were read by physicians different from those who read the x-rays and ultrasounds. Inclusion/exclusion criteria not clearly stated. No independent reference standard.	
Crippa et al., 2000	Metastatic melanoma	English J Nucl Med	Include	Inclusion/exclusion criteria not clearly stated. 38 patients followed prospectively. PET scans read in a blinded fashion and re-read retrospectively. No comparison, but sensitivity/specificity with respect to size.	C

Table 38: Methodological Quality of Studies – Head and Neck Cancer

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Di Martino et al., 2000	Head and neck cancer	English Arch Otolaryngol Head Neck Can	Include	50 patients recruited prospectively. Inclusion/exclusion criteria clearly stated. Blinded reading? No mention. Method of interpreting PET scans not explained.	C
Lowe et al., 2000	Recurrent head and neck cancer	English J Clin Oncol	Include	Overlapping of patients with those of another study (44). 30 patients in this study. Inclusion/exclusion criteria not clearly stated. Blinded reading? No mention. Method of interpreting PET scans not explained. PET compared with correlative imaging.	C
Lonneux, 2000	Recurrent head and neck cancer	English Laryngoscope	Include	44 patients recruited prospectively. Inclusion/exclusion	C

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
				criteria. Blinded reading. PET compared with morphological imaging.	
Jungehulsing et al., 2000	Unknown primary with manifestation in the head and neck lymph nodes	English Otolaryngol Head & Neck Surg	Include	27 patients with unknown primary. Inclusion/exclusion criteria not clearly stated. No mention of blinded reading.	C
Bohuslavizki et al., 2000	Unknown primary	English J Nucl Med	Include	Knowledge of clinical, surgical and histopathologic findings and correlative imaging were used to assess the PET scan. 53 patients evaluated retrospectively.	D
Perie et al., 2000	Unknown primary	English Ann Otol Rhinol Laryngol	Exclude	N/A	N/A
Lassen et al., 1999	Unknown primary	English Eur J Cancer	Include	20 patients. Knowledge of correlative imaging findings, histological findings and localization information on metastases available at the time of PET scan interpretation.	D
Farber et al., 1999	Recurrent head and neck cancer	English Laryngoscope	Include	Retrospective, 28 patients. Two readers visually analyzed the PET images. No mention of blinded reading.	C

Table 39: Methodological Quality of Studies – Lymphoma

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Jerusalem et al., 1999	Hodgkin's and non-Hodgkin's lymphoma	English Blood	Include	Prospective recruitment. CT performed upon abnormal PET findings. PET scans examined by a single investigator.	C
Buchmann et al., 2001	Lymphoma	English	Include	52 patients Reference test per-	B

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
		Cancer		formed within 2 weeks following PET. Discrepant results were verified by biopsy. Blinded reading.	
Hueltenschmidt et al., 2001	Lymphoma	English Cancer	Include	81 patients. Inclusion/exclusion criteria not given. Conventional methods used irregularly.	C
Jerusalem et al., 2000	Lymphoma	English Haematologica	Include	Only 28 patients. No comparison.	D
Spaepen et al., 2001	Lymphoma	English Journal of Clinical Oncology	Include	93 patients. Pre- and posttreatment evaluation. Blinded reading.	B
Tatsumi et al., 2001	Lymphoma	English Journal of Nuclear Medicine	Include	Small sample (30 patients). CT performed within 2 weeks following PET. Blinded reading.	C

Table 40: Methodological Quality of Studies – Breast Cancer

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Cook and Fogelman 1999	Breast - metastases	English Sem Nucl Med	Exclude	N/A	N/A
Crippa et al., 1997	Breast - metastases	English Tumori	Include	Only 16 cases without the disease. 31 axillary lymph nodes + /52 axillary nodes -. Inclusion/exclusion criteria not given. Patient characteristics not given.	C
Cowen, 1998	Breast - metastases	French Cancer/Radiotherapie	Exclude	N/A	N/A
Noh et al., 1999	Breast cancer	English Eur J Surg	Exclude	N/A	N/A
Crippa et al., 1998	Breast cancer	English J Nucl Med	Include	Consecutive patients with palpable nodules; 27 nodes +/ 45 nodes -. PET images interpreted in a blinded fashion. PET compared with pathology report.	B
Raylman et al., 2000	Breast cancer	English Med Phys	Exclude	N/A	N/A

Table 41: Methodological Quality of Studies – Prostate Cancer

STUDY	DETECTION OF:	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Seltzer et al., 1999	Prostate cancer	English J Urol	Include	PET images examined by 2 investigators who were not blinded to each other but who were blinded to the findings of the monoclonal antibody scans. Reference standard somewhat circular. Prospective recruitment.	C

Table 42: Methodological Quality of Studies – Other Applications (not examined in this report)

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Flamen et al., 2000	Esophageal cancer	English J Clin Oncol	Include	74 patients reviewed prospectively. Inclusion/exclusion criteria clearly stated. The images were interpreted blinded to patient data.	B
Meltzer et al., 2000	Esophageal cancer	English Clin Nucl Med	Include	47 patients. PET images reviewed by 2 nuclear medicine clinicians. CT scans read by one radiologist in a blinded fashion. Exclusion criteria.	C
Choi et al., 2000	Esophageal cancer	English J Nucl Med	Include	61 consecutive patients studied prospectively. 100 N+, 282 N-. PET and CT scans read by clinicians in a blinded fashion, by consensus. Inclusion criteria clearly stated.	B
Tiepolt et al., 2000	Thyroid cancer	English Ann Nucl Med	Include	31 patients. Reading of coincidence gamma camera scans blinded to PET scans. PET not compared with conventional imaging.	D
Lips et al., 2000	Thyroid cancer metastases	English Netherl J Med	Exclude	N/A (case reports of 4 patients).	N/A
Schulte et al., 2000	Skeletal tumors	English J Nucl Med	Include	202 patients. Inclusion/exclusion criteria given. Protocol clearly described. PET images read by two independent clinicians blinded to clinical data. Diagnosis determined by surgical specimen. PET not compared with conventional imaging.	C
Barkheet et al., 2000	Breast infection and inflammation	English Clin Nucl Med	Exclude	N/A	N/A
Barkheet et al., 1999	Benign esophageal disease	English Clin Nucl Med	Exclude	N/A	N/A
Stumpe et al., 2000	Soft-tissue and bone infections	English Eur J Nucl Med	Include	Patients with clinical symptoms of infection. Small sample (39 patients); 40+ and 12- lesions.	C

Table 43: Methodological Quality of Studies – Neurology

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
Reiman et al., 2001	Alzheimer's disease	English Proc. Natl. Acad. Sci. USA	Exclude	N/A	N/A
Kawano et al. , 2001	Alzheimer's disease	English Dementia and Geriatrix Cognitive Disorders	Exclude	N/A	N/A
Dupont et al., 2000	Epilepsy	English Arch Neurol	Include	30 consecutive patients. Comparison with postsurgical outcome.	C
Muzik et al., 2000	Epilepsy	English Neurology	Include	Very small sample (n=10). No mention of blinded reading. FDG-PET compared with FMZ-PET and with intracranial EEG.	C
Ryvlin et al., 1998	Epilepsy	English Brain	Include	100 consecutive patients, 12 controls. Blinded interpretation. FDG-PET, FMZ-PET and MRI. FDG-PET and FMZ-PET were performed on the same day.	B
Hwang et al., 2001	Epilepsy	English AJNR Am J Neurol	Include	117 patients. Blinded interpretation SPECT, MRI, pathology. Both tests were performed on the same day.	B
Bader et al., 1999	Recurrent glioma	English Eur J Nucl Med	Include	Confirmation of recurrence. 30 patients. Interpretation of PET and SPECT blinded to clinical or histopathologic findings. Comparison with SPECT.	B
DeWitte *et al.*, 2001	Glioma (high-grade astrocytoma)	English J Neurooncol	Include	Tumor grading. 91 patients. No comparison with conventional imaging. Blinded reading. No sensitivity data.	C
Derlon *et al.*, 2000	Glioma (oligodendrogliomas)	English Eur J Nucl Med	Include	FDG compared with MET. 47 patients. Comparison with MRI + CT.	C

STUDY	SITE	LANGUAGE AND SOURCE	INCLUDE OR EXCLUDE	COMMENTS	METHODOLOGICAL QUALITY
				Blinded reading.	
Eary et al., 1999	Malignant brain tumors	English Cancer Res	Include	FDG compared with MET. 13 patients. No mention of blinded reading. No sensitivity data.	C
Nuutinen et al., 2000	Glioma (astrocytoma)	English Int J Radiat Oncol Biol Phys	Include?	^{11}C-MET PET only. 14 patients. Comparison with conventional imaging. Blinded reading.	C
Sato et al., 1999	Glioma	English (**ABSTRACT**) Neuro Surg Rev	Include?	^{11}C-MET PET only. 13 patients.	C?
Stokkel et al., 1999	Recurrent brain tumors	English (**ABSTRACT**) Nucl Med Comm	Include	16 patients Comparison with SPECT. No mention of blinded reading in abstract.	C?
Roelcke et al., 1999	Glioma (low-grade astrocytoma)	English J Neurol Neuro Surg Psychiatry	Include	30 patients. FDG compared with MET. No mention of blinded reading. No sensitivity data (tumor-to-contralateral brain uptake ratios).	C

Appendix 10

PET Cost Components

APPENDIX 10: PET COST COMPONENTS

Table 44: Purchase prices (cyclotron + PET)
(taxes not included)
[Source: AMSMNQ, 2000]

Cyclotron:		$2.5 to $3.8 million
Positron emission tomograph:		$1.8 to $3.2 million
Radiochemistry/radiopharmacy facilities:		$300,000
Equipment and nonrecurrent expenses:		$200,000
Construction costs:	Depend on the site.	
Total:		$4.8 to $7.5 million + construction costs and taxes

Table 45: Purchase prices (PET without cyclotron)
(taxes not included)
[Source: AMSMNQ, 2000]

Positron emission tomograph:	$1.8 to $3.2 million
Equipment and nonrecurrent expenses:	$100,000
Construction costs:	$200,000 to $400,000
Total:	$1.9 to 3.3 million + construction costs and taxes

Remodelling (or construction) costs: vary considerably according to the site.

Example:

For a cyclotron, about $250,000 for self-shielded models and about $1 million if a vault needs to be built. Depending on the site, the costs can therefore vary substantially.

For a scanner, about $100,000 if the space is already available. More, depending on the remodelling needs not associated with the scanner. Related equipment (monitors, scanners, shielding): about $250,000. Anticipate different impacts, depending on the type of equipment. Example 1: Models with BGO crystals need to be cooled with water. The costs will be similar to those of a CT scanner (cold water circuit with water from the hospital. They can easily be higher if the circuit does not already exist.

Example 2: ADAC* scanners are installed in an air-conditioned room that requires special cooling.

---

* ADAC Laboratories is part of Phillips Medical Systems, a worldwide supplier of diagnostic imaging equipment.

Table 46: Operating costs (cyclotron + PET)

(This figure is calculated for the output of a single site, at the rate of 1,500 scans a year. The output of other sites requires additional equipment and personnel expenses.)

[Source: AMSMNQ, 2000; modified by Dr. F. Bénard, May 2001]

Salaries and employee benefits	
Technologists (2):	$101,840
Secretary's office/reception:	$32,382
Cyclotron operator:	$50,000
Chemistry technician:	$50,000
Radiochemist:	$80,000
Radiopharmacist (14 hrs/wk):	$25,775
Nursing support (1 day/month):	$2,665
Total salaries:	$342,662
Equipment and supplies	
Supplies:	$35,000
Laboratory reagents:	$100,000
Film:	$3,000
Recording paper:	$1,000
Laundry:	$1,000
Parts, maintenance:	$25,000
Biomedical waste equipment:	$2,400
Office supplies:	$2,400
Total equipment and supplies:	$169,800
Maintenance contracts/costs	
Cyclotron:	(service contract) $150,000
PET:	(service contract) $210,000
Total maintenance contracts:	$360,000
Grand total:	$872,462

Table 47: Operating costs (PET without cyclotron)

(This figure is for about 1,000 scans a year.)

[Source: AMSMNQ, 2000, modified by Dr. F. Bénard, May 2001]

Salaries and employee benefits	
Technologists (2):	$101,840
Secretary's office/reception:	$32,382
Nursing support (1 day/period):	$2,665
Total salaries:	$136,887
Equipment and supplies	
Radiopharmaceuticals:	$350,000
Supplies:	$35,000
Film:	$3,000
Recording paper:	$1,000
Laundry:	$1,000
Parts, maintenance:	$25,000
Biomedical waste equipment:	$1,200
Office supplies:	$2,400
Total equipment and supplies:	$418,600
Maintenance contracts/costs	
PET:	$180,000
Total maintenance contracts:	
Grand total:	$735,487

Appendix 11

Economic Models: Additional Information

APPENDIX 11: ECONOMIC MODELS: ADDITIONAL INFORMATION

Figure 4: Decision tree (lung cancer)

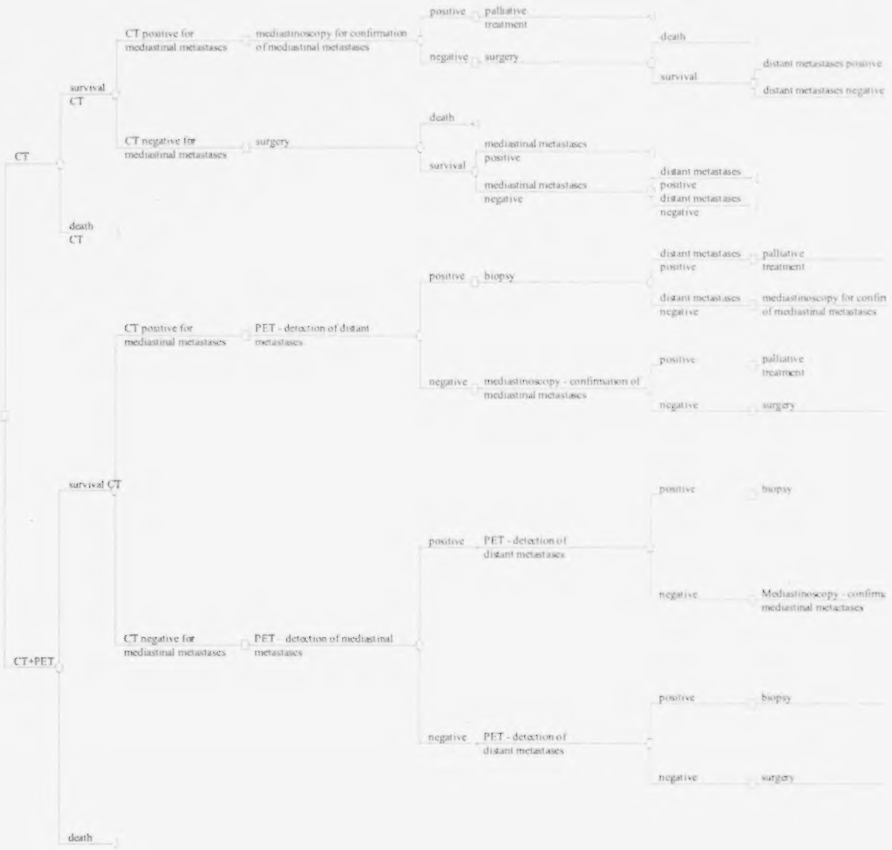

positive
palliative treatment
CT positive for mediastinal metastases
mediastinoscopy for confirmation of mediastinal metastases
death
negative
surgery
distant metastases positive
survival
survival CT
distant metastases negative
death
CT negative for mediastinal metastases
surgery
mediastinal metastases positive
CT
survival
distant metastases positive
mediastinal metastases negative
distant metastases negative
death CT
distant metastases positive
palliative treatment
positive
biopsy
distant metastases negative
mediastinoscopy for confin of mediastinal metastases
CT positive for mediastinal metastases
PET - detection of distant metastases
positive
palliative treatment
negative
mediastinoscopy - confirmation of mediastinal metastases
negative
surgery
survival CT
positive
biopsy
positive
PET - detection of distant metastases
negative
Mediastinoscopy - confirms mediastinal metactases
CT negative for mediastinal metastases
PET – detection of mediastinal metastases
CT+PET
positive
biopsy
negative
PET - detection of distant metastases
negative
surgery
death

Table 48: Variables, intervals and predefined distributions for the Monte Carlo analysis (lung cancer)

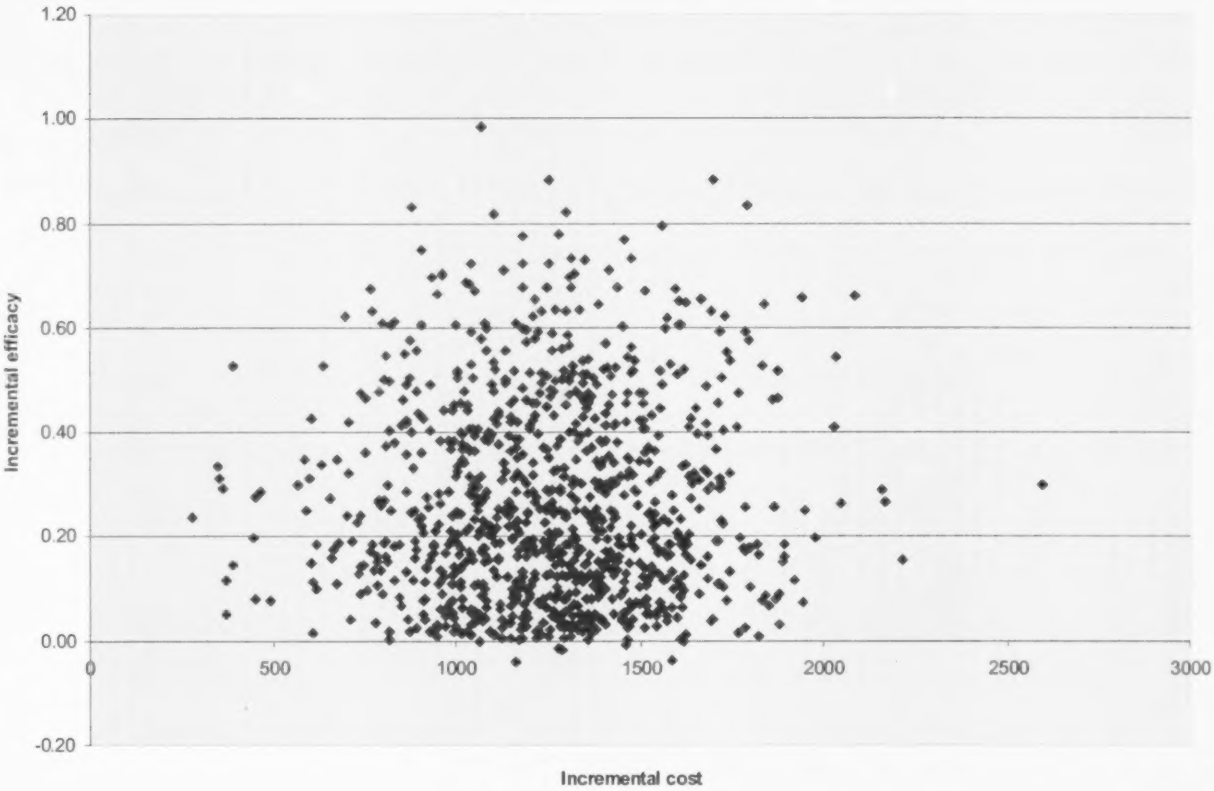
Variable	Baseline value	Lower limit	Upper limit	Distribution
Cost* of hospital stay for mediastinoscopy	5,054	4,549	5,559	Normal, 20% variance
Cost of surgery	8,424	7,582	9,266	Normal, 20% variance
Cost of hospital stay for biopsy	6,130	5,517	6,743	Normal, 20% variance
Cost of hospital stay for mediastinoscopy, biopsy and surgery	9,163	8,247	10,079	Normal, 20% variance
Sensitivity of CT	0.75	0.6	0.9	Triangular
Specificity of CT	0.66	0.55	0.77	Triangular
Life expectancy** of patients who receive palliative treatment	1	0.1	2	Uniform
Life expectancy of patients who are treated surgically	7	1	15	Uniform
Surgical mortality rate	0.03	0.02	0.2	Uniform
Sensitivity of PET in detecting distant metastases	0.82	0.64	1	Triangular
Specificity of PET in detecting distant metastases	0.93	0.88	0.98	Triangular
Sensitivity of PET in detecting mediastinal metast.	0.91	0.81	1	Triangular
Specificity of PET in detecting mediastinal metast.	0.86	0.78	0.94	Triangular
Probability of metastases detected by PET	0.07	0.05	0.11	Uniform
Prevalence	0.31	0.28	0.38	Uniform

* In Canadian dollars
** In years

Table 49: Univariate sensitivity analysis (lung cancer)

		Incremental cost-effectiveness ratio
Baseline scenario		4,689
Surgical mortality rate		
	0.02	4765
	0.04	4821
	0.06	4878
	0.08	4937
	0.1	4997
Prevalence		
	0.15	4925
	0.2375	4788
	0.325	4842
	0.4125	5031
	0.5	5358
Cost of stay for surgery alone		
	7544	5376
	8603.25	4742
	9662.5	4109
	10721.75	3475
	11781	2841
Cost of stay for surgery and mediastinoscopy		
	7609	4489
	8743.5	4635
	9878	4781
	11012.5	4927
	12147	5073
Surgical mortality rate		
	0	4599
	0.05	4751
	0.1	4915
	0.15	5089
	0.2	5277
Life expectancy of patients who receive palliative treatment		
	0.1	4118
	0.575	4401
	1.05	4725
	1.525	5101
	2	5542
Life expectancy of patients who are treated surgically		
	1	724242
	4.5	5267
	8	2643
	11.5	1764
	15	1324
Specificity of PET in detecting mediastinal metastases		
	0.65	7080
	0.7	7099
	0.75	7118
	0.8	7137
	0.85	7156
Sensitivity of PET in detecting distant metastases		
	0.64	3145
	0.73	3113
	0.82	3082
	0.91	3051
	1	3019
Specificity of PET in detecting distant metastases		
	0.73	3226
	0.7975	3177
	0.865	3128
	0.9325	3080
	1	3032
Probability of distant metastases detected by PET		
	0.05	2660
	0.065	2962
	0.08	3359
	0.095	3901
	0.11	4689

Figure 5: Monte Carlo analysis: 1,000 simulations (lung cancer)



Each point on the graph represents the result of a simulation. The horizontal axis represents the incremental cost, the vertical axis the incremental efficacy.

Table 50: Monte Carlo analysis (lung cancer): mean, median and quartiles

		Incremental cost	Incremental efficacy	Incremental cost-effectiveness ratio
Mean		1,253	0.26	17,666
Median		1,260	0.22	5,342
Quartile	25	1,052	0.12	3,006
	50	1,260	0.22	5,342
	75	1,442	0.39	10,618
	100	2 598	0.99	4,058,550

Table 51: Distribution of incremental cost-effectiveness ratios for the 1,000 Monte Carlo simulations (lung cancer)

Interval (incremental cost-effectiveness ratio)	Percentage
0 to 4 999	46
5,000 to 9,999	26
10,000 to 14,999	9
15,000 to 19,999	4
20,000 to 24,999	3
25,000 to 29,999	2
30,000 to 34,999	2
35,000 to 39,999	1
40,000 to 44,999	1
45,000 to 49,999	1
> 50,000	5
Total	100

Figure 6: Decision tree (myocardial viability)

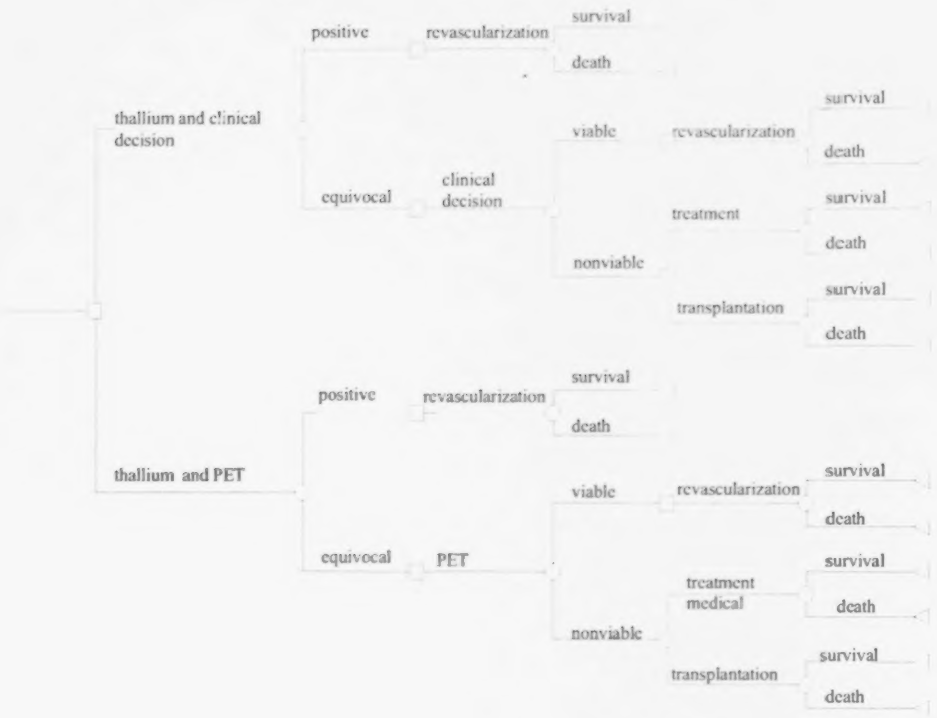
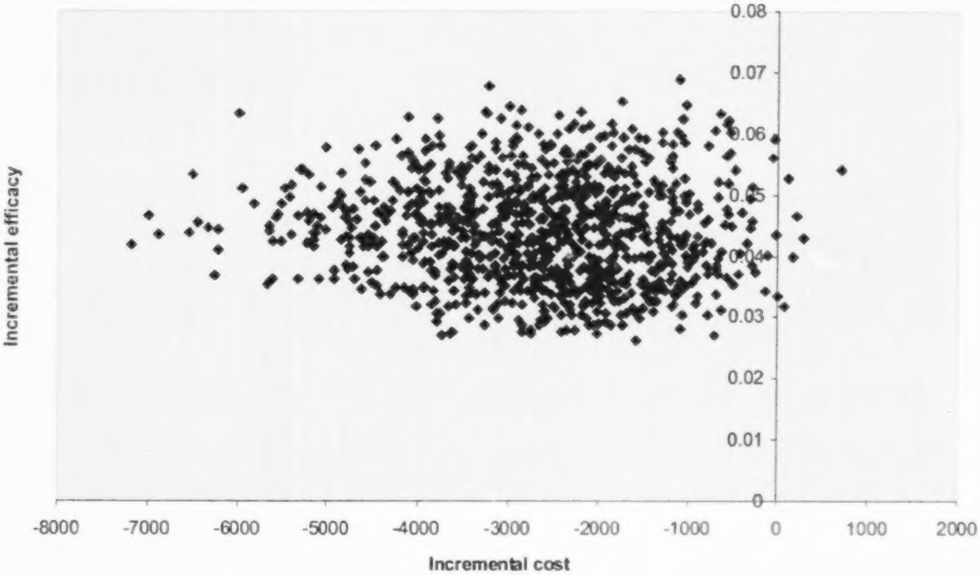

thallium and clinical decision
positive
revascularization
survival
death
equivocal
clinical decision
viable
revascularization
survival
death
nonviable
treatment
survival
death
transplantation
survival
death
thallium and PET
positive
revascularization
survival
death
equivocal
PET
viable
revascularization
survival
death
nonviable
treatment medical
survival
death
transplantation
survival
death

Table 52: List of variables and predefined distributions (myocardial viability)

Description	Distribution
Cost of a PET scan	20% variance, normal
Cost of revascularization	20% variance, normal
Cost of a thallium scan	20% variance, normal
Cost of medical treatment	20% variance, normal
Cost of transplantation	20% variance, normal
5-year probability of survival following revascularization	Baseline value
5-year probability of survival following medical treatment	Baseline value
5-year probability of survival following transplantation	Baseline value
Probability of medical treatment	Uniform
Probability of unequivocal thallium scan	Uniform
Probability of detecting viable myocardium in the context of an equivocal thallium scan in the thallium-alone option	Uniform
Probability of detecting viable myocardium in the context of an equivocal thallium scan in the thallium + PET option	Baseline value

Figure 7: Monte Carlo analysis: 1,000 simulations, detection of myocardial viability



Appendix 12

List of Experts Consulted for the Purpose of Creating the Decision Trees

APPENDIX 12: LIST OF EXPERTS CONSULTED FOR THE PURPOSE OF CREATING THE DECISION TREES

Clinical experts at Hôpital Laval in Québec City were consulted for the purpose of creating the decision trees, determining the explicit probabilities for the variables and determining the population for which PET technology would be used first.

Experts consulted

Specialists in heart failure

- Dr. Marie-Hélène Leblanc
- Dr. Onil Gleeton
- Dr. Denis Coulombe
- Dr. Erik Augustin

Specialist in nuclear medicine

- Dr. Jean Guimont

Specialists in PET

- Dr. Heinrick Schelbert (UCLA at Los Angeles)
- Dr. Paolo Camici (Hammersmith Hospital, London, UK)

References

REFERENCES

REPORTS BY CURRENT OR POTENTIAL USERS

Association des médecins spécialistes en médecine nucléaire du Québec (AMSMNQ) L'utilisation clinique de la tomographie par émission de positrons au Québec. Québec: AMSMNQ, 2000.

Beanlands R, Chamberlain M, et al. Ontario Council of Medical Imaging. Position paper on the future of Positron emission tomography in Ontario. 1999.

Bourgouin P. Association des radiologistes du Québec. Tomographie par émission de positrons - Position de l'Association des radiologistes du Québec. October 14, 2000.

Positron Technology Committee. Reports prepared for the September 26, 2000 meeting (unpublished).

Benkelfat, C. La tomographie par émission de positrons (TEP) en psychiatrie. Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

Bogaty P. "Position Paper": Le point de vue de la cardiologie dans le dossier du PET SCAN. Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

Carmant L. Rôle de la tomographie par émission de positron dans les désordres neurologiques. Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

Couillard P. La tomographie par émission de positrons (TEP) en pratique neurochirurgicale: indications et besoins. Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

Lacasse Y. Tomographie par émission de positrons en oncologie pulmonaire. Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

Laplante J. L'utilisation du Positron en oncologie. Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

Létourneau R. Évaluation du rôle du positron en regard des tumeurs solides (à l'exclusion des tumeurs thoraciques, neurologiques et génito-urinaires). Comité de travail sur la technologie du positron. Montréal: Fédération des médecins spécialistes du Québec, September 2000.

ASSESSMENT REPORTS

Adams E. Evaluating diagnostic tests: A guide to the literature. Boston, MA: Management Decision and Research Center, Health Services Research & Development Service, Office of Research and Development, Department of Veterans Affairs: 1997. Technology Assessment Program Report No.4.

Adams E, Asua J, Conde OJ, Erlichman M, Flynn K, Hurtado-Saracho I, eds. On behalf of INAHTA. Positron emission tomography: Experience with PET and synthesis of the evidence. Stockholm: International Network of Agencies for Health Technology Assessment, 1999.

Adams E, Flynn K, eds. Positron Emission Tomography: descriptive analysis of experience with PET in VA. Boston, MA: Management Decision and Research Center, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs, 1998. Technology Assessment Program Report No.10.

Baffert S, Lajonchère JP, Féry-Lemonnier E, CÉDIT. Tomographie par émission de positrons: état d'avancement du dossier. Paris: Assistance Publique - Hôpitaux de Paris, CÉDIT, 1999.

Blue Cross Blue Shield of Massachusetts. Policy 358: PET scans - positron emission tomography. 2000 [consulted on November 29, 2000]. URL: http://www.bcbsma.com/hresource/358.htm.

Catalan Agency for Health Technology Assessment (CAHTA). Assessments of clinical PET - various indications (internal document). Barcelona: CAHTA, 1993.

Cowley D, Corabian P, Hailey D. Functional diagnostic imaging in the assessment of myocardial viability. Part 1 - Overview; Part 2 - Details of studies. Edmonton: Alberta Heritage Foundation for Medical Research, 1999.

Medicare Services Advisory Committee. Report of the review of positron emission tomography. Commonwealth of Australia, Department of Health and Aged Care (Diagnostics and Technology Branch): August 2000. URL: http://www.health.gov.au/haf/msac.

Flynn K, Adams E, eds. Positron emission tomography: Descriptive analysis of experience with PET in VA and systematic reviews: FDG-PET as a diagnostic test for cancer and Alzheimer's disease. Boston, MA: Management Decision and Research Center, Health Services Research and Development Service, Office of Research and Development, Department of Veterans Affairs, 1996.

Ghersi D, Howard K, Irwig L, Salkeld G, Simes J, eds. Commonwealth review of positron emission tomography - final assessment report. Commonwealth of Australia. Medicare Services Advisory Committee - Department of Health and Aged Care, March 2000.

HAYES Inc. Positron emission tomography (PET) for other malignancies: colorectal cancer, malignant lymphoma, malignant melanoma, breast cancer - Draft update - Executive summary - Internal document. Lansdale, PA: Winifred S. Hayes, Inc., 1999. Report number: none.

HAYES Inc. Positron emission tomography (PET) for cardiac applications - Draft update - Executive summary - Internal document. Lansdale, PA: Winifred S. Hayes, Inc., 1999. Report number: none.

Lozano JP, de la Blanca E, Briones P, eds. Tomografia de emision de positrones (PET): sintesis de investigacion sobre efectividad en diferentes indicaciones clinicas. Seville: Agencia de Evaluacion de Tecnologias Sanitarias de Andalucia, 2000.

Minnesota Health Technology Advisory Committee. Positron emission tomography (PET) for oncologic applications [Web page]. October 2000. URL: http://www.health.state.mn.us/htac/pet.htm.

Robert G, Milne R, eds. Health Technology Assessment, NHS R&D HTA Programme. Positron emission tomography: establishing priorities for health technology assessment. Health Technol Assessment 1999;3(16).

Tunis S, Stojak M, Richardson S et al., eds. FDG positron emission tomography - CAG-00065 - Decision memorandum. Baltimore, MD: U.S. Department of Health and Human Services, Health Care Financing Administration, coverage and Analysis Group, 2000.

INDIVIDUAL REFERENCES

Acland KM, O'Doherty MJ, Russell-Jones R. The value of positron emission tomography scanning in the detection of subclinical metastatic melanoma. J Am Acad Dermatol 2000;42(4):606-11.

Akinboboye OO, Idris O, Cannon PJ, Bergmann SR. Usefulness of positron emission tomography in defining myocardial viability in patients referred for cardiac transplantation. Am J Cardiol 1999 Apr;83(8):1271-4,A9.

Allen-Auerbach M, Schoder H, Johnson J, et al. Relationship between coronary function by positron emission tomography and temporal changes in morphology by intravascular ultrasound (IVUS) in transplant recipients. J Heart Lung Transplant 1999;18(3):211-9.

Allman K, Wieland D, Muzik O, et al. Carbon-11 hydroxyephedrine with positron emission tomography for serial assessment of cardiac adrenergic neuronal function after acute myocardial infarction in humans. J Am Coll Cardiol 1993;22:368-75.

Almkvist O, Winblad B. Early diagnosis of Alzheimer dementia based on clinical and biological factors. Eur Arch Psychiatry Clin Neurosci 1999;249 Suppl 3:3-9.

Alzheimer Society of Canada. La maladie d'Alzheimer - Statistiques. [Web page], 2001. URL: http://www.alzheimer.ca/french/disease/ statspeople.htm. (consulted in April 2001).

Anzai Y, Carroll WR, Quint DJ et al. Recurrence of head and neck cancer after surgery or irradiation: prospective comparison of 2-deoxy-2-[F-18]fluoro-D-glucose PET and MR imaging diagnosis. Radiology 1996;200:135-141.

Arrighi JA, Ng CK, Dey HM, Wackers FJ, Soufer R. Effect of left ventricular function on the assessment of myocardial viability by technetium-99m sestamibi and correlation with positron emission tomography in patients with healed myocardial infarcts or stable angina pectoris, or both. Am J Cardiol 1997;80(8):1007-13.

Avril N, Scheidhauer K, Kuhn W. Breast cancer. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000a, pp. 355-72.

Avril N, Weber W, Breul J. Prostate cancer. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000b, pp. 287-98.

Bader JB, Samnick S, Moringlane JR, Feiden W, Schaefer A, Kremp S, et al. Evaluation of l-3-[123I]iodo-alpha-methyltyrosine SPET and fluorodeoxyglucose PET in the detection and grading of recurrences in patients pretreated for gliomas at follow-up: a comparative study with stereotactic biopsy. Eur J Nucl Med. 1999 Feb;26(2):144-51.

Baer FM, Voth E, Deutsch HJ, Schneider CA, Horst M, de Vivie ER, et al. Predictive value of low dose dobutamine transesophageal echocardiography and fluorine-18 fluorodeoxyglucose positron emission tomography for recovery of regional left ventricular function after successful revascularization. J Am Coll Cardiol 1996 Jul;28(1):60-9.

Baller D, Notohamiprodjo G, Gleichmann U, Holzinger J, Weise R, Lehmann J. Improvement in coronary flow reserve determined by positron emission tomography after 6 months of cholesterol-lowering therapy in patients with early stages of coronary atherosclerosis. Circulation 1999;99(22):2871-5.

Bangerter M, Kotzerke J, Griesshammer M, Elsner K, Reske SN, Bergmann L. Positron emission tomography with 18-fluorodeoxyglucose in the staging and follow-up of lymphoma in the chest. Acta Oncol 1999;38(6):799-804.

Bangerter M, Moog F, Buchmann I, Kotzerke J, Griesshammer M, Hafner M, Elsner K, Frickhofen N, Reske SN, Bergmann L. Whole-body 2-[18F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for accurate staging of Hodgkin's disease. Ann Oncol. 1998 Oct;9(10):1117-22.

Banta HD, McNeil BJ. Evaluation of the CAT scanner and other diagnostic technologies. Health Care Manage Rev 1978 Winter;3(1):7-19.

Bares R, Galonska P, Dempke W, Handt S, Bull U, Osieka R. Somatostatin receptor scintigraphy in malignant lymphoma: first results and comparison with glucose metabolism measured by positron-emission tomography. Horm Metab Res Suppl. 1993;27:56-8.

Barkhcet SM, Amin T, Alia A-G, Kuzo R, Powe J. F-18 FDG uptake in benign esophageal disease. Clin Nucl Med 1999;24(12):995-7.

Barkhcet SM, Powe J. Benign causes of 18-FDG uptake on the whole body imaging. Sem Nucl Med 1998;XXVIII(4):352-58.

Barkhcet SMB, Powe J, Kandil A, Ezzat A, Rostom A, Amartey J. F-18 FDG uptake in breast infection and inflammation. Clin Nucl Med 2000;25:100-3.

Baum RA, Rutter CM, Sunshine JH, Blebea JS, Blebea J, Carpenter JP, et al. Multicenter trial to evaluate vascular magnetic resonance angiography of the lower extremity. American College of Radiology Rapid Technology Assessment Group. JAMA 1995 Sep;274(11):875-80.

Bax JJ, Cornel JH, Visser FC, Fioretti PM, van Lingen A, Reijs AE, et al. Prediction of recovery of myocardial dysfunction after revascularization. Comparison of fluorine-18 fluorodeoxyglucose/thallium-201 SPECT, thallium-201 stress-reinjection SPECT and dobutamine echocardiography. J Am Coll Cardiol 1996 Sep;28(3):558-64.

Bax JJ, Poldermans D, Elhendy A, Boersema E, Rahimtoola SH. Sensitivity, specificity and predictive accuracies of various noninvasive techniques for detecting hibernating myocardium. Curr Probl Cardiol 2001 Feb;26(2):141-86.

Bax JJ, van Eck-Smit BL, van der Wall EE. Assessment of tissue viability: clinical demand and problems. Eur Heart J 1998 Jun;19(6):847-58.

Beanlands RS, deKemp RA, Smith S, Johansen H, Ruddy TD. F-18-fluorodeoxyglucose PET imaging alters clinical decision making in patients with impaired ventricular function. Am J Cardiol 1997 Apr;79(8):1092-5.

Beanlands RS. Outcome and cost-effectiveness of FDG-PET in LV dysfunction (PARR 2). University of Ottawa Heart Institute, 2000-2001.

Beck JR, Kassirer JP, Pauker SG. A convenient approximation of life expectancy (the "DEALE"). I. Validation of the method. Am J Med 1982;73(6):883-8.

Begg CB, Greenes RA, Iglewicz B. The influence of uninterpretability on the assessment of diagnostic tests. J Chronic Dis 1986;39(8):575-84.

Begg CB, Greenes RA. Assessment of diagnostic tests when disease verification is subject to selection bias. Biometrics 1983 Mar;39(1):207-15.

Begg CB, McNeil BJ. Assessment of radiologic tests: control of bias and other design considerations. Radiology 1988 May;167(2):565-9.

Begg CB. Biases in the assessment of diagnostic tests. Stat Med 1987 Jun;6(4):411-23.

Begg CB. Experimental design of medical imaging trials. Issues and options. Invest Radiol 1989 Nov;24(11):934-6.

Begg CB. Methodologic standards for diagnostic test assessment studies. J Gen Intern Med 1988 Sep-Oct;3(5):518-20.

Beller GA. Noninvasive assessment of myocardial viability. N Engl J Med 2000;343(20):1488-90.

Bénard F, Smith RJ, Hustinx R, Karp JS, Alavi A. Clinical evaluation of processing techniques for attenuation correction with ^{137}Cs in whole-body PET imaging. J Nucl Med 1999a;40(8):1257-63.

Bénard F, Sterman D, Smith RJ, Kaiser LR, Albelda SM, Alavi A. Prognostic value of FDG PET imaging in malignant pleural mesothelioma. J Nucl Med 1999b;40(8):1241-5.

Bender H, Strachler-Pohl HJ. PET in head and neck tumors. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag; 2000. Pp. 155-68.

Bengel FM, Schwaiger M. Nuclear medicine studies of the heart. Eur Radiol 1998;8(9):1698-706.

Bengel FM, Ueberfuhr P, Ziegler S, Nekolla S, Reichart B, Schwaiger M. Serial assessment of sympathetic reinnervation after orthotopic heart transplantation. A longitudinal study using PET and C-11 Hydroxyephedrine. Circulation 1999;99:1866-71.

Bennett DA. Part I. Epidemiology and public health impact of Alzheimer's disease. Dis Mon 2000a;46(10):657-65.

Bennett DA. Part II. Clinical diagnosis and course of Alzheimer's disease. Dis Mon 2000b;46(10): 666-86.

Berlangieri SU, Scott AM, Knight SR, et al. F-18 fluorodeoxyglucose positron emission tomography in the non-invasive staging of non-small cell lung cancer. Eur J Cardio-Thoracic Surg 1999;16(suppl. 1):S25-S30.

Blessing C, Feine U, Geiger L, Carl M, Rassner G, Fierlbeck G. Positron emission tomography and ultrasonography. A comparative retrospective study assessing the diagnostic validity in lymph node metastases of malignant melanoma. Arch Dermatol 1995;131:1394-8.

Bohuslavizki KH, Klutmann S, Kröger S, Sonnemann U, Buchert R, Werner JA, et al. FDG PET detection of unknown primary tumors. J Nucl Med 2000;41(5):816-22.

Bonow RO. Identification of viable myocardium. Circulation. 1996 Dec;94(11):2674-80.

Braunwald E, Rutherford JD. Reversible ischemic left ventricular dysfunction: evidence for the "hibernating myocardium". J Am Coll Cardiol 1986 Dec;8(6):1467-70.

Brundage BH, Massie BM, Botvinick EH. Improved regional ventricular function after successful surgical revascularization. J Am Coll Cardiol 1984 Apr;3(4):902-8.

Buchmann I, Reinhardt M, Elsner K, Bunjes D, Altehoefer C, Finke J, et al. 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. A bicenter trial. Cancer 2001 Mar 1;91(5):889-99.

Bury T, Barreto A, Daenen F, Barthelemy N, Ghaye B, Rigo P. Fluorine-18 deoxyglucose positron emission tomography for the detection of bone metastases in patients with non small cell lung cancer. Eur J Nucl Med 1998;25(9):1244-7.

Calkins H, Allman K, Bolling S, et al. Correlation between scintigraphic evidence of regional sympathetic neuronal dysfunction and ventricular refractoriness in the human heart. Circulation 1993a;88:172-9.

Calkins H, Lehmann MH, Allman K, et al. Scintigraphic pattern of regional cardiac sympathic innervation in patients with familial long QT syndrome using positron emission tomography. Circulation 1993b;87:1616-21.

Camici PG. Positron emission tomography and myocardial imaging. Heart 2000 Apr;83(4):475-80.

Campisi R, Czernin J, Schoder H, et al. L-arginine normalizes coronary vasomotion in long-term smokers. Circulation 1999b;99:491-497.

Campisi R, Nathan L, Pampaloni MH, et al. Effect of chronic hormone replacement therapy on coronary vasomotion in post-menopausal women. Circulation 1999a;100(suppl I):I-221.

Carr R, Barrington SF, Madan B, O'Doherty MJ, Saunders CA, van der Walt J, Timothy AR. Detection of lymphoma in bone marrow by whole-body positron emission tomography. Blood. 1998 May 1;91(9):3340-6.

Carrel T, Jenni R, Haubold-Reuter S, von Schulthess G, Pasic M, Turina M. Improvement of severely reduced left ventricular function after surgical revascularization in patients with preoperative myocardial infarction. Eur J Cardiothorac Surg 1992;6(9):479-84.

Chalmers TC. PET scans and technology assessment. JAMA. 1988 Nov 11;260(18):2713-5.

Chatterjee K, Swan HJ, Parmley WW, Sustaita H, Marcus HS, Matloff J. Influence of direct myocardial revascularization on left ventricular asynergy and function in patients with coronary heart disease. With and without previous myocardial infarction. Circulation 1973 Feb;47(2):276-86.

Chee MW, Morris HH 3rd, Antar MA, et al. Presurgical evaluation of temporal lobe epilepsy using interictal temporal spikes and positron emission tomography. Arch Neurol 1993;50(1):45-8.

Choi JY, Lee KH, Shim YM, Lee KS, Kim JJ, Kim SE, et al. Improved detection of individual nodal involvement in squamous cell carcinoma of the esophagus by FDG PET. J Nucl Med 2000; 41(5):808-15.

Choudhury L, Elliott P, Rimoldi O, et al. Transmural myocardial blood flow distribution in hypertrophic cardiomyopathy and effect of treatment. Basic Res Cardiol 1999;94(1):49-59.

Choudhury L, Guzzetti S, Lefroy DC, et al. Myocardial beta adrenoceptors and left ventricular function in hypertrophic cardiomyopathy. Heart 1996;75:50-4.

Cook GJ, Fogelman I. Skeletal metastases from breast cancer: imaging with nuclear medicine. Semin Nucl Med 1999;29(1):69-79.

Cooper LS, Chalmers TC, McCally M, Berrier J, Sacks HS. The poor quality of early evaluations of magnetic resonance imaging. JAMA. 1988 Jun 10;259(22):3277-80.

Cowley D, Corabian P, Hailey D. Functional diagnostic imaging in the assessment of myocardial viability. Part 1 - Overview; Part 2 - Details of studies. Edmonton: Alberta Heritage Foundation for Medical Research, 1999.

Crippa F, Agresti R, Donne VD, Pascali C, Bogni A, Chiesa C, et al. The contribution of positron emission tomography (PET) with 18F- fluorodeoxyglucose (FDG) in the preoperative detection of axillary metastases of breast cancer: the experience of the National Cancer Institute of Milan. Tumori 1997;83(2):542-3.

Crippa F, Agresti R, Seregni E, Greco M, Pascali C, Bogni A, et al. Prospective evaluation of fluorine-18-FDG PET in presurgical staging of the axilla in breast cancer. J Nucl Med 1998; 39(1):4-8.

Crippa F, Leutner M, Belli F, Gallino F, Greco M, Pilotti S, et al. Which kinds of lymph node metastases can FDG PET detect? A clinical study in melanoma. J Nucl Med 2000;41(9):1491-4.

Cummings SR, Lillington GA, Richard RJ. Estimating the probability of malignancy in solitary pulmonary nodules. A Bayesian approach. Am Rev Respir Dis 1986;134(3):449-52.

Czernin J, Barnard J, Sun K, *et al.* Effect of short-term cardiovascular conditioning and low fat diet on myocardial blood flow and flow reserve. Circulation 1995;92:197-204.

de Wit M, Bumann D, Beyer W, Herbst K, Clausen M, Hossfeld DK. Whole-body positron emission tomography (PET) for diagnosis of residual mass in patients with lymphoma. Ann Oncol. 1997; 8 Suppl 1:57-60.

De Witte O, Lefranc F, Levivier M, Salmon I, Brotchi J, Goldman S. FDG-PET as a prognostic factor in high-grade astrocytoma. J Neurooncol. 2001 Sep;49(2):157-63.

Delbeke D, Lawrence SK, Abou-Khalil BW, Blumenkopf B, Kessler RM. Postsurgical outcome of patients with uncontrolled complex partial seizures and temporal lobe hypometabolism on 18FDG-positron emission tomography. Invest Radiol 1996;31(5):261-6.

Delbeke D,Vitola JV, Sandler MP, Arildsen RC, Powers TA, Wright JK Jr, et al. Staging recurrent metastatic colorectal carcinoma with PET. J Nucl Med 1997;38:1196-1201.

Derlon JM, Chapon F, Noel MH, Khouri S, Benali K, Petit-Taboue MC, Houtteville JP, Chajari MH, Bouvard G. Non-invasive grading of oligodendrogliomas: correlation between in vivo metabolic pattern and histopathology. Eur J Nucl Med. 2000 Jul;27(7):778-87.

Deshmukh A, Scott JA, Palmer EL, Hochberg FH, Gruber M et Fischman AJ. Impact of fluorodeoxyglucose positron emission tomography on the clinical management of patients with glioma. Clin Nucl Med 1996;21:720-5.

Devous MD Sr, Thisted RA, Morgan GF, Leroy RF, Rowe CC. SPECT brain imaging in epilepsy: a meta-analysis. J Nucl Med 1998;39(2):285-93.

Dewan NA, Reeb SD, Gupta NC, Gobar LS, Scott WJ. PET-FDG imaging and transthoracic needle lung aspiration biopsy in evaluation of pulmonary lesions. A comparative risk-benefit analysis. Chest 1995;108(2):441-6.

Dewan NA, Shehan CJ, Reeb SD, Gobar LS, Scott WJ, Ryschon K. Likelihood of malignancy in a solitary pulmonary nodule: comparison of Bayesian analysis and results of FDG-PET scan. Chest 1997;112(2):416-22.

Dhital K, Saunders CAB, Seed PT, O'Doherty MJ, Dussek J. [F-18]fluorodeoxyglucose positron emission tomography and its prognostic value in lung cancer. Eur J Cardio Thorac Surg 2000; 18(4):425-8.

Di Carli MF, Asgarzadie F, Schelbert HR, Brunken RC, Laks H, Phelps ME, Maddahi J. Quantitative relation between myocardial viability and improvement in heart failure symptoms after revascularization in patients with ischemic cardiomyopathy. Circulation 1995 Dec;92(12): 3436-44.

Di Carli MF, Davidson M, Little R, Khanna S, Mody FV, Brunken RC, et al. Value of metabolic imaging with positron emission tomography for evaluating prognosis in patients with coronary artery disease and left ventricular dysfunction. Am J Cardiol 1994 Mar;73(8):527-33.

Di Carli MF, Maddahi J, Rokhsar S, Schelbert HR, Bianco-Batlles D, Brunken RC, Fromm B. Long-term survival of patients with coronary artery disease and left ventricular dysfunction: implications for the role of myocardial viability assessment in management decisions. J Thorac Cardiovasc Surg 1998 Dec;116(6):997-1004.

Di Carli MF, Tobes MC, Manger T, et al. Effects of cardiac sympathetic innervation on coronary blood flow. N Engl J Med 1997;336:1208-15.

Dietlein M, Krug B, Groth W, Smolarz K, Scheidhauer K, Psaras T, et al. Positron emission tomography using 18F-fluorodeoxyglucose in advanced stages of malignant melanoma: a comparison of ultrasonographic and radiological methods of diagnosis. Nucl Med Commun 1999;20(3):255-61.

Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, Schicha H. Cost-effectiveness of FDG-PET for the management of potentially operable non small cell lung cancer: priority for a PET-based strategy after nodal-negative CT results. Eur J Nucl Med. 2000b Nov;27(11):1598-609.

Dietlein M, Weber K, Gandjour A, Moka D, Theissen P, Lauterbach KW, Schicha H. Cost-effectiveness of FDG-PET for the management of solitary pulmonary nodules: a decision analysis based on cost reimbursement in Germany. Eur J Nucl Med. 2000a Oct;27(10):1441-56.

Dillemans B, Deneffe G, Verschakelen J, Decramer M. Value of computed tomography and mediastinoscopy in preoperative evaluation of mediastinal nodes in non small cell lung cancer. A study of 569 patients. Eur J Cardiothorac Surg 1994; 8(1):37-42.

Di Martino E, Nowak B, Hassan HA, et al. Diagnosis and staging of head and neck cancer - A comparison of modern imaging modalities (positron emission tomography, computed tomography, color-coded duplex sonography) with panendoscopic and histopathologic findings. Arch Otolar Head Neck Surgery 2000;126(12):1457-61.

Dimitrakopoulou-Strauss A. Colorectal carcinomas. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000, pp. 235-254.

Duong TH, Hendi P, Fonarow G, Asgarzadie F, Stevenson L, Di Carli M, et al. Rôle of positron emission tomography assessment of myocardial viability in the management of patients who are referred for cardiac transplantation. Circulation 1995 October 15;92(8):I-123.

Dreyfus GD, Duboc D, Blasco A, Vigoni F, Dubois C, Brodaty D, et al. Myocardial viability assessment in ischemic cardiomyopathy: benefits of coronary revascularization. Ann Thorac Surg 1994 Jun;57(6):1402-7;discussion 1407-8.

Dupont S, Semah F, Clemenceau S, Adam C, Baulac M, Samson Y. Accurate prediction of postoperative outcome in mesial temporal lobe epilepsy: a study using positron emission tomography with 18fluorodeoxyglucose. Arch Neurol 2000 Sep;57(9):1331-6.

Dwamena BA, Sonnad SS, Angobaldo JO, Wahl RL. Metastases from non small cell lung cancer: mediastinal staging in the 1990s--meta-analytic comparison of PET and CT. Radiology 1999; 213(2):530-6.

Eary JF, Mankoff DA, Spence AM, Berger MS, Olshen A, Link JM, O'Sullivan F, Krohn KA. 2-[C-11]thymidine imaging of malignant brain tumors. Cancer Res. 1999 Feb 1;59(3):615-21.

Eigtved A, Andersson AP, Dahlstrom K, Rabol A, Jensen M, Holm S, et al. Use of fluorine-18 fluorodeoxyglucose positron emission tomography in the detection of silent metastases from malignant melanoma. Eur J Nucl Med 2000;27(1):70-5.

Eitzman D, al-Aouar Z, Kanter HL, vom Dahl J, Kirsh M, Deeb GM, Schwaiger M. Clinical outcome of patients with advanced coronary artery disease after viability studies with positron emission tomography. J Am Coll Cardiol 1992 Sep;20(3):559-65.

Elefteriades JA, Tolis G, Levi E, Mills LK, Zaret BL. Coronary artery bypass grafting in severe left ventricular dysfunction: excellent survival with improved ejection fraction and functional state. J Am Coll Cardiol 1993 Nov;22(5):1411-7.

Engel J Jr, Henry TR, Risinger MW, et al. Presurgical evaluation for partial epilepsy: relative contributions of chronic depth-electrode recordings versus FDG-PET and scalp-sphenoidal ictal EEG. Neurology 1990 40:1670-7.

Epilepsy Canada. Épidémiologie [Web web]. 1998; URL: http://www.epilepsy.ca/fran/epidemioFR.html. (consulted in April 2001).

Erasmus JJ, McAdams HP, Rossi SE, Goodman PC, Coleman RE, Patz EF. FDG PET of pleural effusions in patients with non small cell lung cancer. Am J Roentgenol 2000;175(1):245-9.

Evans EW. Resection for bronchial carcinoma in the elderly. Thorax 1973 Jan;28(1):86-8.

Farber LA, Benard F, Machtay M, Smith RJ, Weber RS, Weinstein GS, et al. Detection of recurrent head and neck squamous cell carcinomas after radiation therapy with 2-18F-fluoro-2-deoxy-D-glucose positron emission tomography. Laryngoscope 1999;109(6):970-5.

Fath-Ordoubadi F, Pagano D, Marinho NV, Keogh BE, Bonser RS, Camici PG. Coronary revascularization in the treatment of moderate and severe postischemic left ventricular dysfunction. Am J Cardiol 1998;82(1):26-31.

Feinstein AR. Meta-analysis and meta-analytic monitoring of clinical trials. Stat Med 1996;15(12):1273-80;discussion 1281-3.

Feinstein AR. Problems, pitfalls, and opportunities in long-term randomized trials. Arzneimittelforschung 1989;39(8A):980-3;discussion 984-5.

Ferrie CD, Maisey M, Cox T, et al. Focal abnormalities detected by 18FDG PET in epileptic encephalopathies. Arch Dis Child 1996;75(2):102-7.

Flamen P, Lerut A, Van Cutsem E, De Wever W, Peeters M, Stroobants S, et al. Utility of positron emission tomography for the staging of patients with potentially operable esophageal carcinoma. J Clin Oncol 2000;18(18):3202-10.

Flamen P, Stroobants S, Van Cutsem E, Dupont P, Bormans G, De Vadder N, et al. Additional value of whole-body positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose in recurrent colorectal cancer. J Clin Oncol 1999;17:894-901.

Flamen P, VanCutsem E, Mortelmans L. A new imaging technique for colorectal cancer: positron emission tomography. Semin Oncol 2000;27(5): 22-9.

Fryback DG, Thornbury JR. The efficacy of diagnostic imaging. Med Decis Making 1991;11(2):88-94.

Gambhir SS, Barrio JR, Phelps ME, et al. Imaging adenoviral-directed reporter gene expression in living animals with positron emission tomography. Proc Natl Acad Sci U S A 1999;96:2333-8

Gambhir SS, Czernin J, Schwimmer J, Silverman DHS, Coleman E, Phelps ME. A tabulated summary of the FDG PET literature. J Nucl Med 2001;42(5, suppl.):1S-93S.

Gambhir SS, Hoh CK, Phelps ME, Madar I, Maddahi J. Decision tree sensitivity analysis for cost-effectiveness of FDG-PET in the staging and management of non small-cell lung carcinoma. J Nucl Med 1996;37(9):1428-36.

Gambhir SS, Shepherd JE, Shah BD, et al. Analytical decision model for the cost-effective management of solitary pulmonary nodules. J Clin Oncol 1998;16(6):2113-25.

Garber AM, Solomon NA. Cost-effectiveness of alternative test strategies for the diagnosis of coronary artery disease. Ann Intern Med 1999;130(9): 719-28.

Gatsonis CA. Random-effects models for diagnostic accuracy data. Acad Radiol 1995 Mar;2(Suppl 1):S14-21;discussion S57-67, S61-4.

Gerber BL, Vanoverschelde JL, Bol A, Michel C, Labar D, Wijns W, Melin JA. Myocardial blood flow, glucose uptake, and recruitment of inotropic reserve in chronic left ventricular ischemic dysfunction. Implications for the pathophysiology of chronic myocardial hibernation. Circulation 1996 Aug;94(4):651-9.

Ginsberg RJ, Hill LD, Eagan RT, et al. Modern thirty-day operative mortality for surgical resections in lung cancer. J Thorac Cardiovasc Surg 1983; 86(5):654-8.

Goldstein DS, Chang PC, Eisenhofer G, et al. Positron emission tomographic imaging of cardiac sympathetic innervation and function. Circulation 1990;81:1606-21.

Gould K, Martucci J, Goldberg D, et al. Short-term cholesterol lowering decreases size and severity of perfusion abnormalities by positron emission tomography after dipyridamole in patients with coronary artery disease: a potential non invasive marker of healing coronary endothelium. Circulation 1994;89:1530-38.

Gould K, Ornish D, Scherwitz L, et al. Changes in myocardial perfusion abnormalities by positron emission tomography after long-term, intense risk factor modification. JAMA 1995;274:894-901.

Gould MK, Maclean CC, Kuschner WG, Rydzak CE, Owens DK. Accuracy of positron emission tomography for diagnosis of pulmonary nodules and mass lesions: a meta-analysis. JAMA 2001; 285(7):914-24.

Grandin C, Wijns W, Melin JA, Bol A, Robert AR, Heyndrickx GR, et al. Delineation of myocardial viability with PET. J Nucl Med 1995 Sep;36(9): 1543-52.

Greven KM, Williams DW 3rd, Keyes JW Jr, McGuirt WF, Watson NE Jr, Case LD. Can positron emission tomography distinguish tumor recurrence from irradiation sequelae in patients treated for larynx cancer? Cancer J Sci Am. 1997 Nov-1997 Dec 31;3(6):353-7.

Gropler RJ, Geltman EM, Sampathkumaran K, Perez JE, Moerlein SM, Sobel BE, et al. Functional recovery after coronary revascularization for chronic coronary artery disease is dependent on maintenance of oxidative metabolism. J Am Coll Cardiol 1992 Sep;20(3):569-77.

Gropler RJ, Geltman EM, Sampathkumaran K, Perez JE, Schechtman KB, Conversano A, et al. Comparison of carbon-11-acetate with fluorine-18-fluorodeoxyglucose for delineating viable myocardium by positron emission tomography. J Am Coll Cardiol 1993 Nov;22(6):1587-97.

Gross BH, Glazer GM, Orringer MB, Spizarny DL, Flint A. Bronchogenic carcinoma metastatic to normal-sized lymph nodes: frequency and significance. Radiology 1988;166(1 Pt 1):71-4.

Gross MW, Weber WA, Feldmann HJ, Bartenstein P, Schwaiger M, Molls M. The value of F-18-fluorodeoxyglucose PET for the 3-D radiation treatment planning of malignant gliomas. Int J Radiat Oncol Biol Phys 1998;41(5):989-95.

Guethlin M, Kasel AM, Coppenrath K, et al. Delayed response of myocardial flow reserve to lipid-lowering therapy with fluvastatin. Circulation 1999;99:475-81.

Gupta NC, Graeber GM, Bishop HA. Comparative efficacy of positron emission tomography with fluorodeoxyglucose in evaluation of small (<1 cm), intermediate (1 to 3 cm), and large (>3 cm) lymph node lesions. Chest 2000;117(3):773-8.

Gupta NC, Graeber GM, Rogers JS 2nd, Bishop HA. Comparative efficacy of positron emission tomography with FDG and computed tomographic scanning in preoperative staging of non small cell lung cancer. Ann Surg 1999;229(2):286-91.

Haas F, Haehnel CJ, Picker W, Nekolla S, Martinoff S, Meisner H, Schwaiger M. Preoperative positron emission tomographic viability assessment and perioperative and postoperative risk in patients with advanced ischemic heart disease. J Am Coll Cardiol 1997 Dec;30(7):1693-700.

Hanasono MM, Kunda LD, Segall GM, et al. Uses and limitations of FDG positron emission tomography in patients with head and neck cancer. Laryngoscope 1999;109:880-5.

Hara T, Inagaki K, Kosaka N, Morita T. Sensitive detection of mediastinal lymph node metastasis of lung cancer with C-11-choline PET. J Nucl Med 2000;41(9):1507-13.

Hartman GW, Hattery RR, Written D, Williamson B Jr. Mortality during excretory urography. Mayo Clinic experience. Am J Roentgenol 1982 Nov;139(5):919-22

Hellman C, Schmidt DH, Kamath ML, Anholm J, Blau F, Johnson WD. Bypass graft surgery in severe left ventricular dysfunction. Circulation 1980 Aug;62(2 Pt 2):I103-10.

Higashi K, Ueda Y, Ayabe K, Sakurai A, Seki H, Nambu Y, et al. FDG PET in the evaluation of the aggressiveness of pulmonary adenocarcinoma: correlation with histopathological features. Nucl Med Commun 2000;21(8):707-14.

Hillman BJ, Gatsonis C, Sullivan DC. American College of Radiology Imaging Network: new national cooperative group for conducting clinical trials of medical imaging technologies. Radiology 1999 Dec;213(3):641-5.

Hochberg MS,Parsonnet V, Gielchinsky I, Hussain SM. Coronary artery bypass grafting in patients with ejection fractions below forty percent. Early and late results in 466 patients. J Thorac Cardiovasc Surg 1983 Oct;86(4):519-27.

Hoh CK, Glaspy J, Rosen P, Dahlbom M, Lee SJ, Kunkel L, Hawkin RA, Maddahi J, Phelps ME. Whole-body FDG-PET imaging for staging of Hodgkin's disease and lymphoma. J Nucl Med 1997 Mar;38(3):343-8.

Holder WD Jr, White RL Jr, Zuger JH, Easton EJ Jr, Greene FL. Effectiveness of positron emission tomography for the detection of melanoma metastases. Ann Surg 1998;227(5):764-9;discussion 769-71.

Hueltenschmidt B, Sautter-Bihl ML, Lang O, Maul FD, Fischer J, Mergenthaler HG, et al. Whole body positron emission tomography in the treatment of Hodgkin disease. Cancer 2001 Jan 15;91(2):302-10.

Hwang SI, Kim JH, Park SW, Han MH, Yu IK, Lee SH, et al. Comparative analysis of MR imaging, positron emission tomography, and ictal single-photon emission CT in patients with neocortical epilepsy. AJNR Am J Neuroradiol 2001 May;22(5):937-46.

Imdahl A, Reinhardt MJ, Nitzsche EU, Mix M, Dingeldey A, Einert A, et al. Impact of 18F-FDG-positron emission tomography for decision making in colorectal cancer recurrences. Langenbecks Arch Surg 2000;385(2):129-34.

Irwig L, Macaskill P, Glasziou P, Fahey M. Meta-analytic methods for diagnostic test accuracy. J Clin Epidemiol 1995 Jan;48(1):119-30;discussion 131-2.

Jadvar H, Johnson DL, Segall GM. The effect of fluorine-18 fluorodeoxyglucose positron emission tomography on the management of cutaneous malignant melanoma. Clin Nucl Med 2000;25(1):48-51.

Jaeschke R, Guyatt G et Sackett DL. User's guides to the medical literature III. How to use an article about a diagnostic test. A. Are the results of the study valid? Evidence-Based Medicine Working Group. J Am Med Assoc 1994;271:389-91.

Jaeschke RZ, Meade MO, Guyatt GH, Keenan SP, Cook DJ. How to use diagnostic test articles in the intensive care unit: diagnosing weanability using f/Vt. Crit Care Med 1997 Sep;25(9):1514-21.

Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P, Fillet G. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. Blood 1999;94(2):429-33.

Jerusalem G, Beguin Y, Fassotte MF, Najjar F, Paulus P, Rigo P et al. Persistent tumor 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma. Haematologica 2000 Jun;85(6):613-8.

Jungehulsing M, Scheidhauer K, Damm M, Pietrzyk U, Eckel H, Schicha H, Stennert E. 2[F]-fluoro-2-deoxy-D-glucose positron emission tomography is a sensitive tool for the detection of occult primary cancer (carcinoma of unknown primary syndrome) with head and neck lymph node manifestation. Otolaryngol Head Neck Surg 2000 Sep;123(3):294-301.

Kao CH, ChangLai SP, Chieng PU, et al. detection of recurrent or persistent nasopharyngeal carcinomas after radiotherapy with 18-fluoro-2-deoxyglucose positron emission tomography and comparison with computed tomography. J Clin Oncol 1998;16:3550-5.

Kawano M, Ichimiya A, Ogomori K, Kuwabara Y, Sasaki M, Yoshida T, Tashiro N. Relationship between both IQ and Mini-Mental State Examination and the regional cerebral glucose metabolism in clinically diagnosed Alzheimer's disease: a PET study. Dement Geriatr Cogn Disord 2001 Mar-Apr 30;12(2):171-6.

Kennedy JW, Kaiser GC, Fisher LD, Fritz JK, Myers W, Mudd JG, Ryan TJ. Clinical and angiographic predictors of operative mortality from the collaborative study in coronary artery surgery (CASS). Circulation 1981 Apr;63(4):793-802.

Kent DL et Larson EB. Diagnostic technology assessments: problems and prospects. Ann Intern Med 1988 May;108(5):759-61.

Kiffer JD, Berlangieri SU, Scott AM, Quong G, Feigen M, Schumer W, et al. The contribution of 18F-fluoro-2-deoxy-glucose positron emission tomographic imaging to radiotherapy planning in lung cancer. Lung Cancer 1998 Mar;19(3):167-77.

Kim RJ, Wu E, Rafael A, Chen EL, Parker MA, Simonetti O, et al. The use of contrast-enhanced magnetic resonance imaging to identify reversible myocardial dysfunction. N Engl J Med 2000 Nov;343(20):1445-53.

Kitsiou AN, Bacharach SL, Bartlett ML, Srinivasan G, Summers RM, Quyyumi AA, Dilsizian V. 13N-ammonia myocardial blood flow and uptake: relation to functional outcome of asynergic regions after revascularization. J Am Coll Cardiol 1999 Mar;33(3):678-86.

Klemenz B, Taaleb KM. Lung Cancer. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000, pp. 193-210.

Knuuti MJ, Saraste M, Nuutila P, Harkonen R, Wegelius U, Haapanen A, et al. Myocardial viability: fluorine-18-deoxyglucose positron emission tomography in prediction of wall motion recovery after revascularization. Am Heart J 1994 Apr; 127(4 Pt 1):785-96.

Krug B, Dietlein M, Groth W, Stützer H, Psaras T, Gossmann A, et al. Fluor-18-fluorodeoxyglucose positron emission tomography (FDG-PET) in malignant melanoma - Diagnostic comparison with conventional imaging methods. Acta Radiologica 2000;41(5):446-52.

Kushwaha SS, Narula J, Narula N, Zervos G, Semigran MJ, Fischman AJ, Alpert NA, Dec GW, Gewirtz H. Pattern of changes over time in myocardial blood flow and microvascular dilator capacity in patients with normally functioning cardiac allografts. Am J Cardiol 1998;82 (11):1377-81.

Kuwert T, Delbeke D. Brain tumours. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag; 2000, p.125-38.

Landoni C, Lucignani G, Paolini G, Zuccari M, Galli L, Di Credico G, et al. Assessment of CABG-related risk in patients with CAD and LVD. Contribution of PET with [18F]FDG to the assessment of myocardial viability. J Cardiovas Surg (Torino) 1999 Jun;40(3):363-72.

Lassen U, Daugaard G, Eigtved A, Damgaard K, Friberg L. 18F-FDG whole body positron emission tomography (PET) in patients with unknown primary tumours (UPT). Eur J Cancer 1999; 35(7):1076-82.

Law MP, Osman S, Pike VW, et al. Evaluation of $[^{11}C]$ GB67, a novel radioligand for imaging myocardial ∂_1-adrenoceptors with positron emission tomography. Eur J Nucl Med 2000;27:7-17.

Lee KS, Marwick TH, Cook SA, Go RT, Fix JS, James KB, et al. Prognosis of patients with left ventricular dysfunction, with and without viable myocardium after myocardial infarction. Relative efficacy of medical therapy and revascularization. Circulation 1994 Dec;90(6):2687-94.

Lefroy DC, de Silva R, Choudhury L, et al. Diffuse reduction of myocardial beta-adrenoceptors in hypertrophic cardiomyopathy: A study with positron emission tomography. J Am Coll Cardiol 1993;22:1653-60.

Leskinen-Kallio S, Ruotsalainen U, Nagren K, Teras M, Joensuu H. Uptake of carbon-11-methionine and fluorodeoxyglucose in non-Hodgkin's lymphoma: a PET study. J Nucl Med 1991 Jun; 32(6):1211-8.

Leung GK, Fan YW, Fong KY. Temporal lobe resection for intractable epilepsy: review of 11 cases. Hong Kong Med J 1999;5(4):329-36.

Lips P, Comans EFI, Hoekstra OS, Clement EV, van-Mourik JC, Teule GJJ. Positron emission tomography for the detection of metastases of differentiated thyroid carcinoma. Neth J Med 2000; 57(4):150-6.

Lonneux M, Lawson G, Ide C, Bausart R, Remacle M, Pauwels S. Positron emission tomography with fluorodeoxyglucose for suspected head and neck tumor recurrence in the symptomatic patient. Laryngoscope 2000;110(9):1493-7.

Lowe VJ, Boyd JH, Dunphy FR, Kim H, Dunleavy T, Collins BT, et al. Surveillance for recurrent head and neck cancer using positron emission tomography. J Clin Oncol 2000;18(3):651-8.

Lowe VJ, Fletcher JW, Gobar L, et al. Prospective investigation of positron emission tomography in lung nodules. J Clin Oncol 1998;16:1075-84.

Lucignani G, Paolini G, Landoni C, Zuccari M, Paganelli G, Galli L, et al. Presurgical identification of hibernating myocardium by combined use of technetium-99m hexakis 2-methoxyisobutyli-sonitrile single photon emission tomography and fluorine-18 fluoro-2-deoxy-D-glucose positron emission tomography in patients with coronary artery disease. Eur J Nucl Med 1992;19(10):874-81.

Maes A, Flameng W, Nuyts J, Borgers M, Shivalkar B, Ausma J, et al. Histological alterations in chronically hypoperfused myocardium. Correlation with PET findings. Circulation 1994 Aug; 90(2):735-45.

Maes AF, Borgers M, Flameng W, Nuyts JL, van de Werf F, Ausma JJ, et al. Assessment of myocardial viability in chronic coronary artery disease using technetium-99m sestamibi SPECT. Correlation with histologic and positron emission tomographic studies and functional follow-up. J Am Coll Cardiol 1997 Jan;29(1):62-8.

Magnani P, Carretta A, Rizzo G, et al. FDG/PET and spiral CT image fusion for mediastinal lymph node assessment of non-small cell lung cancer patients. J Cardiovasc Surg (Torino) 1999;40(5): 741-8.

Manolidis S, Donald PJ, Volk P, et al. The use of positron emission tomography scanning in occult and recurrent head and neck cancer. Acta Otolaryngol Suppl (Stockh) 1998:5341.

Markand ON, Salanova V, Worth R, Park HM, Wellman HN. Comparative study of interictal PET and ictal SPECT in complex partial seizures. Acta Neurol Scand 1997;95(3):129-36.

Marom EM, McAdams HP, Erasmus JJ, Goodman PC, Culhane DK, Coleman RE, et al. Staging non small cell lung cancer with whole-body PET. Radiology 1999;212(3):803-9.

Marwick TH, Shan K, Go RT, MacIntyre WJ, Lauer MS. Use of positron emission tomography for prediction of perioperative and late cardiac events before vascular surgery. Am Heart J 1995 Dec;130(6):1196-202.

Marwick TH, Zuchowski C, Lauer MS, Secknus MA, Williams J, Lytle BW. Functional status and quality of life in patients with heart failure undergoing coronary bypass surgery after assessment of myocardial viability. J Am Coll Cardiol 1999 Mar;33(3):750-8.

McFalls EO, Baldwin D, Kuskowski M, Liow J, Chesler E, Ward HB. Utility of positron emission tomography in predicting improved left ventricular ejection fraction after coronary artery bypass grafting among patients with ischemic cardiomyopathy. Cardiology 2000;93(1-2):105-12.

McLoud TC, Bourgouin PM, Greenberg RW, et al. Bronchogenic carcinoma: analysis of staging in the mediastinum with CT by correlative lymph node mapping and sampling. Radiology 1992;182(2):319-23.

McNeil BJ. Prospects for outcomes research in radiology and health policy. Acad Radiol 1996 Apr;3(Suppl 1):S19-20

McNeil BJ. Technology assessment. Acad Radiol. 1995 Sep;2(Suppl 2):S100-2.

Meltzer CC, Luketich JD, Friedman D, Charron M, Strollo D, Meehan M, et al. Whole-body FDG positron emission tomographic imaging for staging esophageal cancer - Comparison with computed tomography. Clin Nucl Med 2000;25(11):882-7.

Merlet P, Delforge J, Syrota A, et al. Positron emission tomography with ^{11}C CGP-12177 to assess beta-adrenergic receptor concentration in idiopathic dilated cardiomyopathy. Circulation 1993;87: 1169-78.

Mijnhout GS, Hoekstra OS, van Tulder MW, Teule GJ, Deville WL. Systematic review of the diagnostic accuracy of (18)F-fluorodeoxyglucose positron emission tomography in melanoma patients. Cancer 2001;91(8):1530-42.

Moog F. Hodgkin and Non Hodgkin lymphoma. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000, pp.255-72.

Moog F, Kotzerke J, Reske SN. FDG PET can replace bone scintigraphy in primary staging of malignant lymphoma. J Nucl Med. 1999 Sep;40(9):1407-13.

Muzik O, da Silva EA, Juhasz C, Chugani DC, Shah J, Nagy F, et al. Intracranial EEG versus flumazenil and glucose PET in children with extratemporal lobe epilepsy. Neurology 2000 Jan 11; 54(1):171-9.

Nestle U, Walter K, Schmidt S, Licht N, Nieder C, Motaref B, et al. 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: high impact in patients with atelectasis. Int J Radiat Oncol Biol Phys 1999 Jun 1;44(3):593-7.

Noh DY, Yun IJ, Kang HS, Kim YC, Kim JS, Chung JK, Lee DS, Lee MC, Moon WK, Youn YK, Oh SK, Choe KJ. Detection of cancer in augmented breasts by positron emission tomography. Eur J Surg 1999 Sep;165(9):847-51.

Nowak B, Di Martino E, Janicke S, et al. Diagnostic evaluation of malignant head and neck cancer by F-18-FDG PET compared to CT/MRI. Nuklearmedizin 1999;38:312-8.

Nuutinen J, Sonninen P, Lehikoinen P, Sutinen E, Valavaara R, Eronen E, Norrgard S, Kulmala J, Teras M, Minn H. Radiotherapy treatment planning and long-term follow-up with methionine PET in patients with low-grade astrocytoma. Int J Radiat Oncol Biol Phys 2000 Aug 1;48(1):43-52.

Ogunbiyi OA, Flanagan FL, Dehdashti F, Siegel BA, Trask DD, Birnbaum EH, Fleshman JW, Read TE, Philpott GW, Kodner IJ. Detection of recurrent and metastatic colorectal cancer: comparison of positron emission tomography and computed tomography. Ann Surg Oncol 1997;4:613-20.

Okada J, Oonishi H, Yoshikawa K, Itami J, Uno K, Imaseki K, Arimizu N. FDG-PET for predicting the prognosis of malignant lymphoma. Ann Nucl Med 1994 Aug; 8(3):187-91.

Pagano D, Townend JN, Littler WA, Horton R, Camici PG, Bonser RS. Coronary artery bypass surgery as treatment for ischemic heart failure: the predictive value of viability assessment with quantitative positron emission tomography for symptomatic and functional outcome. J Thorac Cardiovasc Surg 1998a Apr;115(4):791-9.

Pagano D, Bonser RS, Townend JN, Ordoubadi F, Lorenzoni R, Camici PG. Predictive value of dobutamine echocardiography and positron emission tomography in identifying hibernating myocardium in patients with postischaemic heart failure. Heart 1998b Mar;79(3):281-8.

Pagley PR, Beller GA, Watson DD, Gimple LW, Ragosta M. Improved outcome after coronary bypass surgery in patients with ischemic cardiomyopathy and residual myocardial viability. Circulation 1997 Aug;96(3):793-800.

Paquet P, Henry F, Belhocine T, Hustinx R, Najjar F, Pierard-Franchimont C, et al. An appraisal of 18-fluorodeoxyglucose positron emission tomography for melanoma staging. Dermatology 2000;200(2):167-9.

Park KC, Schwimmer J, Shepherd JE, et al. Decision analysis for the cost-effective management of recurrent colorectal cancer. Ann Surg 2001;233(3):310-9.

Pasquet A, Lauer MS, Williams MJ, Secknus MA, Lytle B, Marwick TH. Prediction of global left ventricular function after bypass surgery in patients with severe left ventricular dysfunction. Impact of pre-operative myocardial function, perfusion, and metabolism. Eur Heart J 2000 Jan;21(2):125-36.

Pasquet A, Robert A, D'Hondt AM, Dion R, Melin JA, Vanoverschelde JL. Prognostic value of myocardial ischemia and viability in patients with chronic left ventricular ischemic dysfunction. Circulation 1999 Jul;100(2):141-8.

Patterson RE, Eisner RL, Horowitz SF. Comparison of cost-effectiveness and utility of exercise ECG, single photon emission computed tomography, positron emission tomography, and coronary angiography for diagnosis of coronary artery disease. Circulation 1995 Jan 1;91(1):54-65.

Patz EF Jr, Lowe VJ, Goodman PC, Herndon J. Thoracic nodal staging with PET imaging with 18FDG in patients with bronchogenic carcinoma. Chest 1995;108(6):1617-21.

Paulus P, Sambon A, Vivegnis D, et al. 18FDG PET for the assessment of primary head and neck tumors: clinical, computed tomography and histopathological correlation in 38 patients. Laryngoscope 1998;108:1578-83.

Perie S, Talbot JN, Monceaux G, et al. Use of a coincidence gamma camera to detect primary tumor with 18fluoro- 2-deoxy-glucose in cervical lymph node metastases from an unknown origin. Ann Otol Rhinol Laryngol 2000;109(8 Pt 1):755-60.

Phelps ME, Hoffman EJ, Coleman RE, et al. Tomographic images of blood pool and perfusion in brain and heart. J Nucl Med 1976;17(7):603-12.

Phelps ME. PET: The merging of biology and imaging into molecular imaging. J Nucl Med 2000;41(4): 661-81.

Pieterman RM, van Putten JWG, Meuzelaar JJ, John WG, Meuzelaar JJ, et al. Preoperative staging of non small-cell lung cancer with positron-emission tomography. New Engl J Med 2000;343(4):254-61.

Pirich C, Schwaiger M. The clinical role of positron emission tomography in management of the cardiac patient. Rev Port Cardiol 2000;19 Suppl 1:I89-100.

Prauer HW, Weber WA, Romer W, Treumann T, Ziegler SI and Schwaiger M. Controlled prospective study of positron emission tomography using the glucose analogue [18f]fluorodeoxyglucose in the evaluation of pulmonary nodules. Br J Surg 1998;85:1506-11.

Primack SL, Hartman TE, Lee KS, Muller NL. Pulmonary nodules and the CT halo sign. Radiology 1994;190(2):513-5.

Primack SL, Lee KS, Logan PM, Miller RR, Muller NL. Bronchogenic carcinoma: utility of CT in the evaluation of patients with suspected lesions. Radiology 1994;193(3):795-800.

Rahimtoola SH. The hibernating myocardium. Am Heart J 1989 Jan;117(1):211-21.

Ransohoff DF, Feinstein AR. Problems of spectrum and bias in evaluating the efficacy of diagnostic tests. N Engl J Med 1978;299(17):926-30.

Raylman RR, Majewski S, Wojcik R, Weisenberger AG, Kross B, Popov V, Bishop HA. The potential role of positron emission mammography for detection of breast cancer. A phantom study. Med Phys 2000;27(8):1943-54.

Rees G, Bristow JD, Kremkau EL, Green GS, Herr RH, Griswold HE, Starr A. Influence of aortocoronary bypass surgery on left ventricular performance. New Engl J Med 1971 May;284(20): 1116-20.

Rege S, Maass A, Chaiken L, et al. Use of positron emission tomography with fluorodeoxyglucose in patients with extracranial head and neck cancers. Cancer 1994;73:3047-3058.

Reiman EM, Caselli RJ, Chen K, Alexander GE, Bandy D, Frost J. Declining brain activity in cognitively normal apolipoprotein E varepsilon 4 heterozygotes: a foundation for using positron emission tomography to efficiently test treatments to prevent Alzheimer's disease. Proc Natl Acad Sci U S A. 2001 Mar 13;98(6):3334-9.

Rinne D, Baum RP, Hor G, Kaufmann R. Primary staging and follow-up of high risk melanoma patients with whole-body 18F-fluorodeoxyglucose positron emission tomography: results of a prospective study of 100 patients. Cancer 1998;82:1664-71.

Roberts PF, Follette DM, vonHaag D, Park JA, Valk PE, Pounds TR, Hopkins DM. Factors associated with false-positive staging of lung cancer by positron emission tomography. Ann Thorac Surg 2000;70(4):1154-9.

Rodriguez M, Ahlstrom H, Sundin A, Rehn S, Sundstrom C, Hagberg H, Glimelius B. [18F] FDG PET in gastric non-Hodgkin's lymphoma. Acta Oncol 1997;36(6):577-84.

Rodriguez M, Rehn S, Ahlstrom H, Sundstrom C, Glimelius B. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. J Nucl Med. 1995 Oct; 36(10):1790-6.

Roelcke U, von Ammon K, Hausmann O, Kaech DL, Vanloffeld W, Landolt H, et al. Operated low grade astrocytomas: a long term PET study on the effect of radiotherapy. J Neurol Neurosurg Psychiatry 1999 May; 66(5):644-7

Rossetti C, Landoni C, Lucignani G, Garraffa G, Ippolito M, Pepi M, et al. Lack of prognostic value of 99mTc MIBI rest, 18F FDG and 201TL rest/redistribution on PTCA outcome of patients with moderate left ventricle dysfunction. Panminerva 1999 Sep;41(3):199-206.

Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. Panel on Cost-Effectiveness in Health and Medicine. JAMA 1996;276(14):1172-7.

Ryvlin P, Bouvard S, Le Bars D, De Lamerie G, Gregoire MC et al. Clinical utility of flumazenil-PET versus [18F]fluorodeoxyglucose-PET and MRI in refractory partial epilepsy. A prospective study in 100 patients. Brain 1998 Nov;121(Pt 11):2067-81.

Sackett DL. Clinical epidemiology: a basic science for clinical medicine. Boston: Little, Brown, 1991.

Sato N, Suzuki M, Kuwata N, Kuroda K, Wada T, Beppu T, Sera K, Sasaki T, Ogawa A. Evaluation of the malignancy of glioma using 11C-methionine positron emission tomography and proliferating cell nuclear antigen staining. Neurosurg Rev 1999 Dec;22(4):210-4.

Saunders CAB, Dussek JE, O'Doherty MJ, Maisey MN. Evaluation of fluorine-18-fluorodeoxyglucose whole body positron emission tomography imaging in the staging of lung cancer. Ann Thorac Surg 1999;67(3):790-7.

Schafers M, Dutka D, Rhodes CG, et al. Myocardial presynaptic and postsynaptic autonomic dysfunction in hypertrophic cardiomyopathy. Circ Res 1998a;82:57-62.

Schafers M, Wichter T, Lerch H, et al. Cardiac sympathetic innervation in patients with idiopathic right ventricular outflow tract tachycardia. J Am Coll Cardiol 1998b;32:181-6.

Scheidhauer K, Avril N, Bonkowsky VM. Carcinoma of unknown origin. In: Wieler HM et Coleman RE. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000, pp. 169-77.

Schelbert HR. The usefulness of positron emission tomography. Curr Probl Cardiol 1998 Feb;23(2): 69-120.

Schulte M, Brecht-Krauss D, Heymer B, Guhlmann A, Hartwig E, Sarkar MR, et al. Grading of tumors and tumorlike lesions of bone: evaluation by FDG PET. J Nucl Med 2000;41(10):1695-701.

Schwaiger M, Kalff V, Rosenpire K. et al. Noninvasive evaluation of the sympathetic nervous system in the human heart by PET. Circulation 1990a;8:457-64.

Schwaiger M, Hutchins G, Rosenspire K, Haka M, Wieland DM. Quantitative evaluation of the sympathetic nervous system by PET in patient with cardiomyopathy. J Nucl Med 1990b;31:792

Scott WJ, Shepherd J, Gambhir SS. Cost-effectiveness of FDG-PET for staging non small cell lung cancer: a decision analysis. Ann Thorac Surg 1998;66(6):1876-83;discussion 1883-5.

Seltzer MA, Barbaric Z, Belldegrun A, Naitoh J, Dorey F, Phelps ME, et al. Comparison of helical computerized tomography, positron emission tomography and monoclonal antibody scans for evaluation of lymph node metastases in patients with prostate specific antigen relapse after treatment for localized prostate cancer. J Urol 1999;162(4):1322-8.

Siebelink HM, Blanksma PK, Crijns HJ, Bax JJ, van Boven AJ, Kingma T, et al. No difference in cardiac event-free survival between positron emission tomography-guided and single-photon emission computed tomography-guided patient management: a prospective, randomized comparison of patients with suspicion of jeopardized myocardium. J Am Coll Cardiol 2001 Jan; 37(1):81-8.

Silberstein EB. Prevalence of adverse reactions to positron emitting radiopharmaceuticals in nuclear medicine. Pharmacopeia Committee of the Society of Nuclear Medicine. J Nucl Med 1998 Dec;39(12):2190-2.

Spaepen K, Stroobants S, Dupont P, Van Steenweghen S, Thomas J, Vandenberghe P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([18F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is FDG-PET a valid alternative to conventional diagnostic methods?. J Clin Oncol. 2001 Jan 15;19(2):414-9.

Staib L, Schirrmeister H, Reske SN, Beger HG. Is F-18-fluorodeoxyglucose positron emission tomography in recurrent colorectal cancer a contribution to surgical decision making? Amer J Surg 2000;180(1):1-5.

STARD Group. Towards complete and accurate reporting of studies on diagnostic accuracy: the STARD statement. November 17, 2000 (unpublished).

Steinert HC, Huch BR, Buck A, et al. Malignant melanoma: staging with whole-body positron emission tomography and 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 1995;195:705-9.

Stevens MJ, Dayanakli F, Raffel DM, et al. Scintigraphic assessment of regionalized defects in myocardial sympathic innervation and blood flow regulation in diabetic patients with automatic neuropathy. J Am Coll Cardiol 1998a;31:1575-84.

Stevens MJ, Raffel DM, Allman DM, et al. Cardiac sympathetic dysinnervation in diabetes: implications for enhanced cardiovascular risk. Circulation 1998b;98:961-8.

Stevens MJ, Raffel DM, Allman KC, Schwaiger M, Wieland DM. Regression and progression of cardiac sympathetic dysinnervation complicating diabetes: an assessment by C-11 hydroxyephedrine and positron emission tomography. Metabolism 1999;48:92-101.

Stokkel MPM, Hoekstra A, van Rijk PP. The detection of small carcinoma with 18F-FDG using a dual head coincidence camera. Eur J Radiology 1999;32(3):160-2.

Strasberg SM, Dehdashti F, Siegel BA, Drebin JA, Linehan D. Survival of patients evaluated by FDG-PET before hepatic resection for metastatic colorectal carcinoma: a prospective database study. Ann Surg 2001;233(3):293-9.

Stumpe KD, Dazzi H, Schaffner A, von Schulthess GK. Infection imaging using whole-body FDG-PET. Eur J Nucl Med 2000;27(7):822-32.

Stumpe KD, Urbinelli M, Steinert HC, Glanzmann C, Buck A, von Schulthess GK. Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: effectiveness and comparison with computed tomography. Eur J Nucl Med. 1998 Jul;25(7):721-8.

Swartz BE, Tomiyasu U, Delgado-Escueta AV, Mandelkern M, Khonsari A. Neuroimaging in temporal lobe epilepsy: test sensitivity and relationships to pathology and postoperative outcome. Epilepsia 1992;33(4):624-34.

Swets JA, Pickett, RM. Evaluation of diagnostic systems: methods from signal detection theory. New York: Academic Press, 1982.

Tamaki N, Kawamoto M, Tadamura E, Magata Y, Yonekura Y, Nohara R, et al. Prediction of reversible ischemia after revascularization. Perfusion and metabolic studies with positron emission tomography. Circulation 1995 Mar;91(6):1697-705.

Tamaki N, Kawamoto M, Takahashi N, Yonekura Y, Magata Y, Nohara R, et al. Prognostic value of an increase in fluorine-18 deoxyglucose uptake in patients with myocardial infarction: comparison with stress thallium imaging. J Am Coll Cardiol 1993 Nov;22(6):1621-7.

Tamaki N, Ohtani H, Yamashita K, Magata Y, Yonekura Y, Nohara R, et al. Metabolic activity in the areas of new fill-in after thallium-201 reinjection: comparison with positron emission tomography using fluorine-18-deoxyglucose. J Nucl Med 1991 Apr;32(4):673-8.

Tamaki N, Yonekura Y, Yamashita K, Saji H, Magata Y, Senda M, et al. Positron emission tomography using fluorine-18 deoxyglucose in evaluation of coronary artery bypass grafting. Am J Cardiol 1989 Oct;64(14):860-5.

Tamaki N. Imaging of cardiac neuronal and receptor function. J Nucl Cardiol 1997;4:553-4.

Tashiro M, Kubota K, Itoh M, Moser E. Trends in use of positron emission tomography. Lancet 2001 Mar 17;357(9259):886.

Tatlidil R, Luther S, West A, Jadvar H, Kingman T. Comparison of fluorine-18 deoxyglucose and O-15 water PET in temporal lobe epilepsy. Acta Neurol Belg 2000 Dec;100(4):214-20.

Thelen MH, Bares R. Malignant melanoma. In: Wieler HJ, Coleman RE, eds. PET in clinical oncology. Damstadt: Steinkopff Verlag, 2000, pp. 299-308.

Thompson TP, Lunsford LD, Kondziolka D. Distinguishing recurrent tumor and radiation necrosis with positron emission tomography versus stereotactic biopsy. Stereotact Funct Neurosurg. 1999; 73(1-4):9-14.

Tiepolt C, Beuthien-Baumann B, Hliscs R, Bredow J, Kühne A, Kropp J, et al. F-18-FDG for the staging of patients with differentiated thyroid cancer: Comparison of a dual-head coincidence gamma camera with dedicated PET. Ann Nucl Med 2000;14(5):339-45.

Tillisch J, Brunken R, Marshall R, Schwaiger M, Mandelkern M, Phelps M, Schelbert H. Reversibility of cardiac wall-motion abnormalities predicted by positron tomography. New Engl J Med 1986 Apr;314(14):884-8.

Tyler DS, Onaitis M, Kherani A, et al. Positron emission tomography scanning in malignant melanoma. Cancer 2000;89(5):1019-25.

Uberfuhr P, Frey AW, Ziegler S, Reichart B, Schwaiger M. Sympathetic reinnervation of sinus node and left ventricle after heart transplantation in humans: regional differences assessed by heart rate variability and positron emission tomography. J Heart Lung Transplant 2000a Apr;19(4):317-23.

Uberfuhr P, Ziegler S, Schwaiblmair M, Reichart B, Schwaiger M. Incomplete sympathetic reinnervation of the orthotopically transplanted human heart: observation up to 13 years after heart transplantation. Eur J Cardiothorac Surg 2000b; 17(2):161-8.

Valk PE, Abella-Columna E, Haseman MK, Pounds TR, Tesar RD, Myers RW, et al. Whole-body PET imaging with 18F-fluorodeoxyglucose in management of recurrent colorectal cancer. Arch Surg 1999;134(5):503-11;discussion 511-3.

Valk PE, Pounds TR, Hopkins DM, et al. Staging non small cell lung cancer by whole-body positron emission tomographic imaging. Ann Thorac Surg 1995;60(6):1573-81;discussion 1581-2.

Valk PE, Pounds TR, Hopkins DM, Haseman MK. Cost-effectiveness of PET imaging in clinical oncology. Nucl Med and Biol 1996;23:737-43.

van den Berg EK, Popma JJ, Dehmer GJ, Snow FR, Lewis SA, Vetrovec GW, Nixon JV. Reversible segmental left ventricular dysfunction after coronary angioplasty. Circulation 1990 Apr;81(4):1210-6.

Vanoverschelde JL, Wijns W, Borgers M, Heyndrickx G, Depre C, Flameng W, Melin JA. Chronic myocardial hibernation in humans. From bedside to bench. Circulation 1997 Apr;95(7):1961-71.

Vanoverschelde JL, Wijns W, Depre C, Essamri B, Heyndrickx GR, Borgers M, et al. Mechanisms of chronic regional postischemic dysfunction in humans. New insights from the study of noninfarcted collateral-dependent myocardium. Circulation 1993 May;87(5):1513-23.

Vansteenkiste J, Stroobants S, De Leyn P, Verschakelen J, Nackaerts K, Deneffe G, et al. Mediastinal lymph node staging with FDG-PET scan in patients with potentially operable non small cell lung cancer: a prospective analysis of 50 cases. Leuven Lung Cancer Group. Chest 1997 Dec; 112(6):1480-6.

Vansteenkiste JF, Stroobants SG, Dupont PJ, et al. FDG-PET scan in potentially operable non-small cell lung cancer: do anatometabolic PET-CT fusion images improve the localisation of regional lymph node metastases? The Leuven Lung Cancer Group. Eur J Nucl Med 1998;25(11):1495-501.

van Tinteren, H, Hoekstra OS, Smit EF, van den Bergh JH, Schreurs AJ, Stallaert RA, et al. Randomized controlled trial (RCT) to evaluate the cost-effectiveness of positron emission tomography (PET) added to conventional diagnosis in non-small cell lung cancer (NSCLC). Abstract 1885. 2000 Program/Proceedings Abstracts. American Society of Clinical Oncology. URL: http: www.asco.org/prf/me/html/00abstracts/ m_toc.htm

Vanuytsel LJ, Vansteenkiste JF, Stroobants SG, De Leyn PR, De Wever W, Verbeken EK, et al. The impact of (18)F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) lymph node staging on the radiation treatment volumes in patients with non small cell lung cancer. Radiother Oncol 2000;55(3):317-24.

Vesselle H, Schmidt RA, Pugsley JM, et al. Lung cancer proliferation correlates with [F-18]fluorodeoxyglucose uptake by positron emission tomography. Clin Can Res 2000;6(10):3837-44.

vom Dahl J, Altehoefer C, Sheehan FH, Buechin P, Schulz G, Schwarz ER, et al. Effect of myocardial viability assessed by technetium-99m-sestamibi SPECT and fluorine-18-FDG PET on clinical outcome in coronary artery disease. J Nucl Med 1997 May;38(5):742-8.

vom Dahl J, Altehoefer C, Sheehan FH, Buechin P, Uebis R, Messmer BJ, et al. Recovery of regional left ventricular dysfunction after coronary revascularization. Impact of myocardial viability assessed by nuclear imaging and vessel patency at follow-up angiography. J Am Coll Cardiol 1996 Oct;28(4):948-58.

vom Dahl J, Eitzman DT, al-Aouar ZR, Kanter HL, Hicks RJ, Deeb GM, et al. Relation of regional function, perfusion, and metabolism in patients with advanced coronary artery disease undergoing surgical revascularization. Circulation 1994 Nov;90(5):2356-66.

von Schulthess GK, Steinert HC, Dummer R, Weder W. Cost-effectiveness of whole-body PET imaging in non small cell lung cancer and malignant melanoma. Acad Radiol 1998;5 Suppl 2:S300-2.

Wagner JD, Schauwecker D, Davidson D, Coleman JJ 3rd, Saxman S, Hutchins G, et al. Prospective study of fluorodeoxyglucose positron emission tomography imaging of lymph node basins in melanoma patients undergoing sentinel node biopsy. J Surg Oncol 1999;17:1508-15.

Walter SD, Irwig L, Glasziou PP. Meta-analysis of diagnostic tests with imperfect reference standards. J Clin Epidemiol 1999 Oct;52(10):943-51.

Weber WA, Neverve J, Sklarek J, et al. Imaging of lung cancer with fluorine-18 fluorodeoxyglucose: comparison of a dual-head gamma camera in coincidence mode with a full-ring positron emission tomography system. Eur J Nucl Med 1999;26(4):388-95.

White PG, Adams H, Crane MD, Butchart EG. Preoperative staging of carcinoma of the bronchus: can computed tomographic scanning reliably identify stage III tumours? Thorax 1994 Oct;49(10):941-3.

Wieland D, Rosenpire K, Hutchins G, et al. Neuronal mapping of the heart with 6-[18F]fluorometaraminol. J Med Chem 1990;33:956-64.

Wiggers H, Nielsen TT, Bottcher M, Egeblad H, Botker HE. Positron emission tomography and low-dose dobutamine echocardiography in the prediction of postrevascularization improvement in left ventricular function and exercise parameters. Am Heart J 2000 Dec;140(6):928-36.

Wijns W, Vatner SF, Camici PG. Hibernating myocardium. N Engl J Med 1998;339:173-81.

Williams DE, Pairolero PC, Davis CS, et al. Survival of patients surgically treated for stage I lung cancer. J Thorac Cardiovasc Surg 1981;82(1):70-6.

Willkomm P, Bender H, Bangard M, Decker P, Grünwald F, Biersack HJ. FDG PET and immunoscintigraphy with Tc-99m-labeled antibody fragments for detection of the recurrence of colorectal carcinoma. J Nucl Med 2000;41(10):1657-63.

Wolpers HG, Burchert W, van den Hoff J, Weinhardt R, Meyer GJ, Lichtlen PR. Assessment of myocardial viability by use of 11C-acetate and positron emission tomography. Threshold criteria of reversible dysfunction. Circulation 1997 Mar 18;95(6):1417-24.

Wong WL, Chebretton EB, McGurk M, et al. A prospective study of PET-FDG imaging for the assessment of head and neck squamous cell carcinoma. Clin Otolaryngol 1997;22:209-14.

Wong WL, Hussain K, Chebretton E, et al. Validation and clinical application of computer combined computed tomography and positron emission tomography with 2-[18F]-fluoro-2-deoxy-D-glucose head and neck images. Am J Surg 1996;172:628-32.

Wyllie E. Surgical treatment of epilepsy in children. Pediatr Neurol 1998;19(3):179-88.

Yokoyama I, Momomura S, Ohtake T, et al. Improvement of impaired myocardial vasodilatation due to diffuse coronary atherosclerosis in hypercholesterolemics after lipid-lowering therapy. Circulation 1999;100:117-122.

Yoshida K, Gould KL. Quantitative relation of myocardial infarct size and myocardial viability by positron emission tomography to left ventricular ejection fraction and 3-year mortality with and without revascularization. J Am Coll Cardiol 1993 Oct;22(4):984-97.

Young TH, Tang KP, Tang HS, et al. Primary malignant lymphoma of the spine diagnosed by Tc-99m MDP and Ga-67 imaging. Clin Nucl Med 1997;22(4):274-6.

Yusuf S, Zucker D, Peduzzi P, Fisher LD, Takaro T, Kennedy JW, et al. Effect of coronary artery bypass graft surgery on survival: overview of 10-year results from randomised trials by the Coronary Artery Bypass Graft Surgery Trialists Collaboration. Lancet 1994 Aug 27;344(8922):563-70.

Zhang X, Liu X, Shi R, Wu Q, Gao R, Liu Y, et al. Evaluation of the clinical value of combination of 99mTc-MIBI myocardial SPECT and 18F-FDG PET in assessing myocardial viability. Radiat Med 1999 May-Jun;17(3):205-10.

Zhuang H, Sinha P, Pourdehnad M, Duarte PS, Yamamoto AJ, Alavi A. The role of positron emission tomography with fluorine-18-deoxyglucose in identifying colorectal cancer metastases to liver. Nucl Med Commun 2000;21(9):793-8.

Zinzani PL, Magagnoli M, Chierichetti F, Zompatori M, Garraffa G, Bendandi M, et al. The role of positron emission tomography (PET) in the management of lymphoma patients. Ann Oncol. 1999 Oct; 10(10):1181-4.

Zubiate P, Kay JH, Mendez AM. Myocardial revascularization for the patient with drastic impairment of function of the left ventricle. J Thorac Cardiovasc Surg 1977 Jan;73(1):84-6.

Québec
Agence d'évaluation
des technologies
et des modes
d'intervention en santé

Some information on . . .

Positron Emission Tomography (PET)

What is Positron Emission Tomography (PET)?

Positron Emission Tomography (PET) is a three-dimensional medical imaging technology used in nuclear medicine. A radioactive substance is administered to the patient, who is then placed within the viewing field of a scanner that images the distribution of the substance in the organism. PET differs from other medical imaging technologies in that it allows metabolic activity in the tissues and blood flow to be observed.

How does PET work?

PET tracks the distribution of a specific molecule, called a tracer, in the body. To carry out a PET scan, the tracer is labeled with a positron-emitting radioisotope. Positively charged positrons are the anti-particles of the negatively-charged electrons.

A minute amount of tracer is injected into the patient's bloodstream, causing no pain or adverse reactions. The isotopes contained in the tracer release the positrons. As each positron leaves the isotope nucleus, it comes into contact with an electron, causing the annihilation of both particles and the emission of two photons, or light particles, that travel in opposite directions. These photons are simultaneously detected by the PET scanner cameras and the data is fed into a computer, to be converted into a 3-D image of the tissues where the tracer is present.

The tracer is selected according to the specific function of the organism to be observed. For example, to identify cancer cells, a glucose molecule, in which one of the oxygen atoms has been replaced by a Fluorine-18 atom, may be used. This tracer makes it possible to identify areas in the organism where glucose uptake is higher than normal, notably in the case of cancer cells, which have a higher metabolism than normal cells.

Fluorine-18, incorporated into fluorodeoxyglucose (or FDG), is the most commonly used isotope in PET scans. Other isotopes used are Oxygen-15, Nitrogen-13 and Carbon-11.

What type of equipment is required to carry out a PET scan?

A cyclotron

In a PET scan, the patient is injected with a tracer marked with a positron-emitting radioisotope. These radioisotopes are produced by a particle accelerator called a cyclotron. Since cyclotron technology is based on nuclear energy, it must be shielded against radiation.
Most of the isotopes used in PET scans have a very short half-life — from two minutes for Oxygen-15 to 110 minutes for Fluorine-18. PET facilities must therefore be located sufficiently close to a cyclotron to allow the products to be transported in a short time.

A radiochemical laboratory

Once radioisotopes have been generated by the cyclotron, they are combined to the tracer in a radiochemical laboratory.

A PET scanner

After the tracer has been injected, the patient is placed under a PET scanner made up of ring-shaped detectors. This scanner detects the photons (or rays) emitted by the tracer.

A PET scanning facility also requires radiation safety equipment and the necessary computer equipment to process the data and produce 3-D images.

Highly qualified personnel are required to operate a PET scanning facility: a technician, nursing staff, radiopharmacist and nuclear medicine specialist. For cyclotron-equipped facilities, cyclotron operators and radiation chemists are also needed.

What are the main clinical applications of PET technology?

PET has proven to be useful in a variety of medical fields, helping to detect certain types of cancer, cardiac disease and neurological disease. The list of recognized clinical applications of PET continues to grow as the research advances.

Where are Québec's PET scanning facilities located?

Québec has two PET centres, both equipped with a cyclotron. They are located at the Montréal Neurological Institute and at the Centre hospitalier universitaire de Sherbrooke.

How does Québec compare with other countries/provinces in terms of its PET scanning facilities?

Country or province	Number of scanners per million inhabitants
United States	0.4
Canada	
British Columbia	0.3
Ontario	0.3
Québec	0.3
Europe	
Germany	0.9
Belgium*	0.9
France*	0.1
United Kingdom	0.2

Australia*	0.2

---

*Additional acquisitions under way

Various sources, 1999-2001

How much does PET cost?

Acquisition costs		
	Cyclotron	$2.5M to $4.6M
	Dedicated PET scanner	$2M to $3M
Setup costs		
	Cyclotron	$0.25M to $1M
	PET scanner	$0.1M to 0.25M
Other costs		
	Training	TBD
	Operation	Variable
	Medical fees	$250 per scan

Source: Agence d'évaluation des technologies et des modes d'intervention en santé
(AÉTMIS)/Agency for Health Services and Technology Assessment
Tel.: (514) 873-2563
Fax: (514) 873-1369
E-mail: aetmis@aetmis.gouv.qc .ca
Web site: www.aetmis.gouv.qc.ca